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ZINC METABOLISM IN HEPATIC DYSFUNCTION*

I. Serum Zinc Concentrations in Laënnec's Cirrhosis and Their Validation by Sequential Analysis

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THE presence of zinc in living organisms and its essentiality as a nutrient for plants and animals have been recognized for many years.[1,2]

Normal persons take in about 10 to 15 mg. of zinc a day, most of it being excreted in the feces, which contain about 10 mg. a day; about 300 or 400 microgm. a day is excreted in the urine.[3] Most human organs contain zinc, the amounts in different organs varying between 10 and 200 microgm. per gram of wet tissue.[4] The serum zinc concentration has been reported to be decreased in several diseases, notably pernicious anemia.[5]

The first specific biochemical role of zinc was demonstrated in 1940 by Keilin and Mann,[6] who showed it to be present in the enzyme carbonic anhydrase; the function of zinc in metabolism has been viewed largely in this light.

During the last two years it has been demonstrated that carboxypeptidase of beef pancreas and several pyridine nucleotide dependent dehydrogenases, alcohol dehydrogenase of yeast, alcohol dehydrogenase of liver, glutamic dehydrogenase of beef liver and lactic dehydrogenase of rabbit muscle are zinc metalloenzymes.[7-14]

Zinc, therefore, occupies a salient place in the enzymatic chain of cellular respiration and in the elimination of carbon dioxide from the cell.

The human liver contains 50 to 60 microgm. per gram of wet tissue.[15] Alcohol dehydrogenase and glutamic dehydrogenase, both zinc enzymes, are crystallized from liver. For this reason, it was decided to investigate the metabolism of this metal in patients with liver disease.

The present study compares the serum zinc levels of normal persons and patients with severe and mild Laënnec cirrhosis. A hypothesis — *that significant differences between the three groups exist* — was tested. The current methods for testing hypotheses statistically are of an a posteriori nature. An a priori method that has arisen from the fields of quality control and wartime operations research is described by Wald.[16] In the present paper a special form of his method, "the sequential probability ratio test,"[17,18] has been applied for the first time to the solution of this type of biologic problem. The present data demonstrate that the serum zinc concentrations in patients with *severe Laënnec cirrhosis* are markedly decreased.

MATERIALS AND METHODS

Duplicate zinc analyses were performed on 2-ml. aliquots of serum obtained from venous blood. The blood samples were obtained without regard to the fasting state. Blood was drawn into acid-cleaned sterile syringes through special stainless-steel needles‖ to avoid contamination, transferred to an acid-cleaned, dried Pyrex centrifuge tube and allowed to clot.[18] The serum was obtained by centrifugation within an hour of collection, decanted and stored in

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polyethylene tubes at 4°C. Contamination was not encountered.

The procedure for the analysis of zinc has been described.[19] All spectrophotometry was performed with the Beckman Model DU spectrophotometer.

Eight normal females and 32 normal males served as controls. Their ages ranged from twenty to fifty-one years. Thirty-three patients with Laënnec's cirrhosis, 7 females and 26 males, represented the experimental group. Their ages ranged from twenty-nine to eighty-two years. A history of alcoholism or poor diet was regarded as prerequisite to the diagnosis of Laënnec's cirrhosis in the whole group studied. The diagnosis was established by biopsy in 3 cases and by autopsy in 3. The group was further subdivided into "mild" and "severe" types of cirrhosis. For the purpose of this study, "severe" cirrhosis was defined as existent in patients who had the unquestionable signs of hepatic insufficiency, such as jaundice, fetor hepaticus, ascites, splenomegaly, esophageal varices, spider angiomas, loss of body hair, gynecomastia and hepatic coma. A total of 25 patients — 22 males and 3 females — fell into this group.

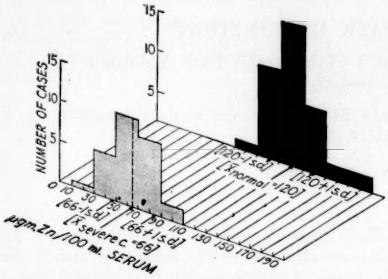

FIGURE 1. *Frequency Distributions of Serum Zinc in 40 Normal Persons and 25 Patients with Severe Cirrhosis. The mean ± 1 standard deviation is indicated for each group.*

Four males and 4 females considered to have "mild" cirrhosis presented a distinct history of alcoholism but had only minimal, though definite, changes and laboratory findings, such as hepatomegaly, transient jaundice and bromsulfalein retention below 22 per cent. This classification was carried out by an unbiased observer who had no knowledge of the serum zinc levels of these patients.

STATISTICAL CONSIDERATIONS AND PROCEDURE

The sequential analytical method that guided the course of this study defines strict limits on the allowed probability of making an erroneous decision. In advance of the experiment, these limits are imposed on and incorporated into the construction of a graphical complex, which consists of an acceptance line, a_m, and a rejection line, r_m, which delineate three mutually exclusive regions: *the region of acceptance; the region of rejection;* and *the region of indifference.* The calculations and mechanics of the procedure have been described[17] and need not be restated here, though a brief summary is given.

After each experimental observation starting with the first, the sum of this and all previous observations is formed, mathematically transformed into the coordinates of the complex and plotted. Successive points are joined to form a *sequential curve* representing all observations. The premises of this test state that no decision can be made as long as this curve pursues a path within the *region of indifference.* But the very first time that the *sequential curve* crosses over into one of the other two regions, the plot indicates that a conclusion has been reached. The decision to accept or reject the initial hypothesis is made, and the experiment is thereby terminated.

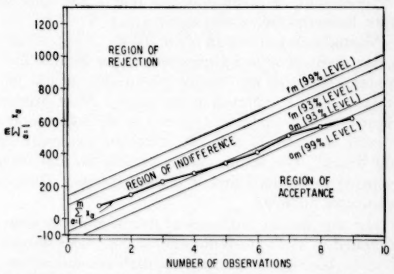

FIGURE 2. *Sequential Probability Ratio Test Applied to the Patients with "Severe" Cirrhosis. The hypothesis that the serum zinc concentrations in these patients is less than 82 microgm. per 100 ml. was proved after 9 observations — valid in 99 out of 100 cases. The procedure is explained in the text.*

RESULTS

Eight successive zinc determinations performed on 1 subject resulted in a mean* $\bar{x}$, of 108 ± 10 microgm. per 100 ml. The distribution of the average values from duplicate zinc determinations on the serums of 40 normal persons are shown in Figure 1. The mean, $\bar{x}_n$ = 120 ± 19 microgm. per 100 ml., includes the biologic and the methodologic variation. Two standard deviations from the mean extend from 82 to 158 microgm. per 100 ml. A χ^2 test showed this to be a normal Gaussian distribution, as expected for a biologic sample of this type. Age, sex, food intake and diurnal variations were not found to be significant variables.

*All data are given as the mean x ± 1 standard deviation from the mean.

Figure 1 shows a histogram for duplicate determinations of 25 patients of the severely cirrhotic group, plotted in a manner similar to those of the normal group. The mean is $\bar{x}_c = 66 \pm 19$ microgm. per 100 ml. The distribution is normal, as shown by the χ^2 test, although the mean is displaced far to the left, being almost half that of the normal population. The standard deviation is identical with that observed for the normal group.

The sequential probability ratio test indicated, after only nine observations, that the mean of the group with severe cirrhosis would fall below 82 microgm. per 100 ml. (Fig. 2). The histogram of Figure 1, based on 25 rather than 9 patients, shows clearly that the prediction of the test was borne out by subsequent results.

The patients classified as having "mild" cirrhosis had a mean serum zinc concentration $\bar{x}_m = 87.8 \pm 20$ microgm. per 100 ml. of serum. The mean of this group is lower than that of the normal group and the distribution is distinctly shifted to lower values, though the standard deviation is nearly identical; it

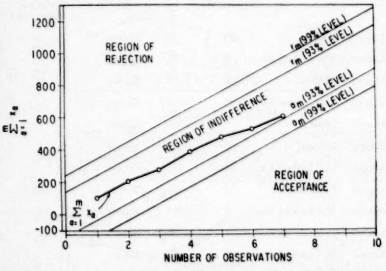

FIGURE 3. *Sequential Probability Ratio Test Applied to the Patients with "Mild" Cirrhosis.*

The hypothesis that the serum zinc concentrations in these cases is less than 101 microgm. per 100 ml. was not proved for 99 out of 100 cases but is valid for less stringent limits of confidence: 93 patients out of 100 could be expected to have serum zinc levels under 101 microgm. per 100 ml. For better statistical proof, more data are needed. The procedure is explained in the text.

cannot be stated, however, that the statistical-significance level of this difference is sufficiently high. The sequential probability ratio test postulate of Figure 3 hypothesized that the mean of this group would fall below 101 microgm. per 100 ml. and would denote a difference from the normal group, which is significant at the 99 per cent level. Figure 3 indicates that more data are needed to ascertain this fact. The pertinent clinical and laboratory data on both groups are shown in Table 1.

Figure 4, giving the serum zinc concentration and the clinical course of 2 patients with severe cirrhosis, is representative of those who improved under observation. Both entered the hospital after prolonged alcoholic bouts. Case 23 presented jaundice and vomiting, and Case 11 vomiting and delirium tremens as the chief complaints. During the two weeks in the hospital and after therapy with vitamins and a high-calorie, high-carbohydrate diet, both showed marked clinical improvement. The serum zinc concentration, low at the time of admission, progressively rose to higher levels concomitant with the patients' improvement.

Discussion

The serum zinc concentrations and the statistical data obtained agree well with those reported by Vikbladh,[5] who, using a similar procedure, found it to be 124 ± 16 microgm. per 100 ml. The observations on patients with cirrhosis indicate a distinct and significant decrease in serum zinc concentrations in this disease.

The classification of patients presented the problem of correlating a single, quantitative parameter, zinc, with the complex, qualitative pattern of a disease. The clinical data and the measurements of serum zinc were therefore grouped independently and by different observers to ascertain whether the low serum metal concentrations could be related to advanced disease. Since no *single* feature of Laënnec's cirrhosis can properly be thought to denote severe disease the combination of signs, symptoms and laboratory findings of unquestionable hepatic insufficiency were judged jointly. Patients with only minimal findings of hepatic insufficiency were eliminated from the group with severe cirrhosis.

The classification, made on the basis of relative serum zinc concentrations, was then correlated with the classification performed independently by clinical judgment. Figures 1 and 2 and the sequential probability ratio test indicate that the two clinical groups differ in their zinc levels and show that the concentration is much higher in those who were "mildly" ill.

This difference was further borne out by the sequential probability ratio test, which applied to the severely ill group tested the hypothesis that the mean of this group would be less than 82 microgm. per 100 ml. of serum, which is more than *two* standard deviations lower than the normal mean. Figure 2 shows that this hypothesis was proved at the 99 per cent level after 9 observations. The "mildly" ill patients, however, were assumed to have a mean less than 101 microgm. per 100 ml.—that is, *one* standard deviation lower than the normal mean. This hypothesis was not borne out at the 99 per cent level of significance after 8 observations. Though a trend in this direction is apparent, many more observations would be required to bear out this premise. This affirms the significance and validity of the classification.

The data presented indicate that the serum zinc concentration is decreased in Laënnec's cirrhosis. The

degree of lowering correlates with the severity of the hepatic dysfunction in these patients. The lowest serum zinc level of 20 microgm. per 100 ml. obtained in this study was measured in a patient (Case 31) who was in deep and fatal hepatic coma (Table 1). — low at the time of admission — subsequently rose to higher levels concomitantly with clinical improvement, further indicating that the serum zinc concentration may be a function of the severity of the disease.

TABLE 1. *Physical Findings, Bromsulfalein Retention and Serum Zinc Concentration of 32 Patients with Laënnec's Cirrhosis.*

Case No.	Patient	Sex	Age	Jaundice	Spider Angiomas	Ascites	Splenomegaly	Coma	Varices	Bromsulfalein Retention	Serum Zinc Concentration	Type of Disease	Comment
			yr.							%	*microgm./100 ml.*		
1	R.F.	F	42	Absent	Absent	Absent	Absent	Absent	Absent	20	100	Mild	Diagnosis confirmed at postmortem examination
2	A.M.	F	73	Present	Absent	Present	Absent	Absent	Absent	*	104	Mild	
3	T.N.	M	67	Absent	Absent	Absent	Absent	Absent	Absent	15	72	Mild	
4	A.B.	F	57	Absent	Absent	Absent	Absent	Absent	Absent	12	112	Mild	
5	M.G.	M	72	Absent	Present	Absent	Absent	Absent	Absent	17	87	Mild	
6	J.F.	M	52	Absent	Absent	Absent	Absent	Absent	Absent	19	50	Mild	
7	J.S.	M	62	Absent	Absent	Present	Absent	Absent	Absent	22	78	Mild	Ascites due to congestive heart failure
8	P.S.	M	58	Present	Present	Present	Present	Absent	Present	25	76	Severe	
9	S.G.	M	56	Present	Present	Present	Present	Absent	Not looked for	*	70	Severe	
10	B.S.	M	60	Present	Present	Absent	Present	Absent	Absent	26	78	Severe	
11	F.H.	M	50	Present	Present	Absent	Absent	Absent	Not looked for	26	53	Severe	
12	B.K.	M	82	Present	Present	Absent	Present	Absent	Present	*	60	Severe	
13	E.C.	M	38	Present	Present	Present	Present	Present	Present	*	70	Severe	
14	J.Z.	M	50	Present	Present	Absent	Present	Absent	Not looked for	76	101	Severe	
15	P.M.	M	72	Present	Present	Present	Present	Absent	Present	52	55	Severe	
16	J.B.	M	63	Present	Present	Absent	Absent	Absent	Not looked for	*	50	Severe	
17	F.R.	F	51	Absent	Present	Absent	Present	Absent	Present	*	96	Severe	
18	J.K.	M	62	Present	Present	Absent	Present	Absent	Not looked for	*	67	Severe	
19	J.P.	M	62	Present	Present	Absent	Absent	Absent	Not looked for	30	72	Severe	
20	R.F.	M	35	Present	Present	Present	Absent	Absent	Present	*	49	Severe	
21	G.P.	M	50	Absent	Present	Absent	Absent	Absent	Absent	*	79	Severe	
22	W.B.	M	41	Present	Present	Absent	Present	Present	Not looked for	*	49	Severe	
23	E.H.	M	49	Present	Present	Absent	Present	Absent	Present	*	61	Severe	
24	C.L.	M	68	Present	Present	Absent	Absent	Absent	Not looked for	46	100	Severe	
25	J.G.	M	30	Present	Present	Present	Present	Present	Present	30	66	Severe	
26	F.R.	F	67	Present	Absent	Absent	Present	Present	Not looked for	*	70	Severe	
27	C.O.	M	60	Present	Present	Absent	Absent	Present	Present	*	80	Severe	
28	J.C.	M	57	Present	Present	Present	Present	Present	Present	*	50	Severe	
29	C.D.	F	54	Present	Present	Absent	Present	Present	Absent	30	46	Severe	
30	A.A.	M	57	Present	Present	Present	Present	Present	Present	*	72	Severe	
31	T.M.	M	43	Present	Present	Present	Present	Present	Present	*	20	Severe	
32	M.M.	M	38	Present	Present	Absent	Absent	Absent	Present	*	76	Severe	

*Test not done.

These facts are illustrated by the data obtained on the 2 patients (Fig. 4) who were under continuous observation and whose clinical status could be assessed accurately. Their serum zinc concentrations

The lowered serum zinc levels seemed to bear a relation to bromsulfalein retention in these patients, though this relation was not found to prevail in cases of liver disease other than cirrhosis. No direct cor-

relation between the lowered serum zinc concentration and other tests of hepatic function in common use was demonstrable. Actually, the over-all clinical judgment appeared to be a better gauge for correlation with serum zinc concentration than the thymol turbidity, serum bilirubin, serum alkaline phosphatase, albumin-globulin ratio and prothrombin time.

It appears at present that the lowered serum zinc is peculiar to patients with Laënnec's cirrhosis in contradistinction to other types of liver disease. Determinations on the serums of 8 patients with infectious hepatitis gave a mean serum zinc concentration of 107 ± 25.4 microgm. per 100 ml. The range was 73 to 165 microgm. per 100 ml. This series is small, but the difference from the normal control group is not striking.

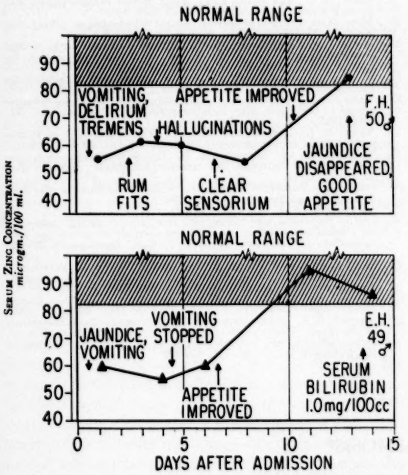

FIGURE 4. *Serum Zinc Concentrations of 2 Patients with Severe Cirrhosis (Case 11 and Case 23, Table 1).*

Both patients improved markedly under observation. The serum zinc concentrations are plotted as a function of time, and the normal range is indicated by crosshatching. The pertinent clinical changes are charted. These patients were treated with a high-calorie, high-vitamin regimen. They were given no additional zinc supplements.

The cause of the depression in serum zinc is not apparent. Little is known concerning the structural association of zinc in human serum and its physiologic control. Vikbladh[5] has studied the problem and reports the presence of two moieties of serum zinc: a loosely bound, dialyzable form, which constitutes 60 per cent of the total serum zinc; and a firmly bound, nondialyzable form, which comprises the remaining 40 per cent. Her data indicate that the decrease in serum zinc concentrations in the patients studied took place at the expense of the loosely bound moiety. The experimental basis for these conclusions are open to serious question, however.

In view of the presence of zinc in alcohol dehydrogenase, glutamic dehydrogenase, carbonic anhydrase and lactic and malic dehydrogenase, serum samples were assayed for these enzyme activities. Only lactic and malic dehydrogenase activities were found, and both were increased in all patients with liver disease.

The differentiation of "normal" and "abnormal" groups is a universal problem of clinical investigation. No adequate scheme for the unequivocal acceptance or rejection of hypotheses has been available. Moreover, the number of observations in the experiment has usually been arbitrary, since statistical decisions are reached after the termination of the experiment.

This study represents a departure from conventional design and interpretation by the introduction of sequential analysis into a problem of clinical investigation, as part of the experimental procedure. This technic regulates the collection of a statistically sufficient number of observations in an efficient manner, simultaneously indicating the conclusion of the experiment. As shown by Wald[16] the test unequivocally settles the validity or lack thereof of the hypothesis under scrutiny at any desired level of significance. If the experiment must be terminated before a very stringent hypothesis is fulfilled, the statistical test parameters may be readjusted to make a decision at whatever level of significance is maximally possible for the observations recorded up to that point.

Sequential analysis requires a concise statement of the problem before experimentation in a form that is both clinically and statistically meaningful. This is well illustrated by the preceding results, which showed that severe cirrhosis is characterized by a mean zinc serum concentration differing from the normal mean by at least two normal standard deviations. Furthermore, continuation of the experiment upheld the conclusions reached by sequential analysis. The mean value in "mild" cirrhosis may differ from the normal value by at least one standard deviation. Although this hypothesis is not accepted at the 99 per cent level of significance, the results so far accumulated would accept it at about the 93 per cent level. The experiment was continued to give this tentative hypothesis as much statistical weight as that advanced about severe cirrhosis.

The presence of zinc in alcohol and glutamic dehydrogenases of liver, as well as the decrease in serum zinc concentration in Laënnec's cirrhosis, raises questions concerning the possible relations between these pathometabolic observations and the disease. The close association of the intake of ethanol to the cirrhotic process has long been the subject of hypothesis and study.[20] The alcohol dehydrogenase of liver is responsible in large measure for the oxidation of ethanol, and the integrity of the enzyme may thus

be cardinal to the preservation of homeostatic hepatic mechanisms. Glutamic dehydrogenase catalyzes the release of ammonia from glutamic acid, which is thereby transformed to alpha-ketoglutaric acid. Excessive accummulation of ammonia is thought by some to have a significant and possibly causal relation to the pathologic physiology and biochemistry of the terminal stages of liver disease and hepatic coma.[21] There is, at present, no experimental evidence that the low serum zinc concentration in cirrhosis reflects a change in the synthesis, degradation, metal content or specific activity of these two or other pyridine dependent metallodehydrogenases of liver. The expansion of these speculative thoughts should lead to the establishment of hypotheses in forms that can be tested by further experimentation.

The data reported here do not allow any extended conclusion concerning the relation of zinc metabolism to Laënnec's cirrhosis. Zinc, however, is a biologically active substance, and the significance of the depression in serum zinc in this disease may yet be revealed in the light of the biochemical functions of this metal.

Summary

The discovery of several zinc dehydrogenases in liver led to the study of zinc metabolism in cirrhosis. Serum zinc concentrations were lowered significantly in patients with cirrhosis of the liver. The concentrations of zinc found bore a relation to the severity of the disease and its fluctuating course. A group of 28 patients with the stigmas of advanced cirrhosis had a serum zinc concentration of 66 ± 19 microgm., as compared to 120 ± 19 microgm. per 100 ml. for a normal group.

The sequential probability ratio test was incorporated into the experimental design and was found to be an important innovation in validation of clinical investigative data.

We are indebted to Miss Lois W. Hersum for technical assistance.

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HISTOPLASMOSIS*

Unraveling the Panamanian Puzzle

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HALF a century has elapsed since Darling,[1] in December, 1905, encountered what is now recognized as the first recorded case of histoplasmosis. Stimulated by the contemporaneous reports two years earlier by Leishman and Donovan on the etiology of kala-azar, and more immediately by Sir Patrick Manson's suggestion (1905) that kala-azar or some analogous disease might exist in America, Darling instituted a careful search for kala-azar in Panama. After an intensive microscopical study of smears from the spleen, liver and rib marrow of all patients with splenomegaly examined at autopsy, he found 3 patients who had died of a disease bearing a close resemblance to kala-azar except for the atypical appearance of the organisms.[2-4] Though recognizing this as a new pathologic entity, he misinterpreted the Leishmania-like organisms and reticuloendothelial involvement as evidence of a tropical disease of protozoan origin, an error perpetuated by his choice of the term *Histoplasma*. Setting the pattern for later writers, he concluded that this was indeed a rare and invariably fatal disease. With complete naïveté he even proposed

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that rapidly improving sanitation in the Canal Zone accounted for the apparent disappearance of any comparable infections in his subsequent investigations.

For years Darling's work evoked little if any interest outside the tropics, but once other cases began to appear, it immediately became obvious that histoplasmosis was not confined within any strict geographic bounds. One by one the rest of Darling's postulates were refuted, even to the extent of proof that the term *capsulatum* was a misnomer, the apparent capsule being an artifact. Concerning its supposed rarity, years ago one could hardly contest the issue in the face of a twenty-year hiatus between Darling's discovery and the next case report,[5,6] and of an additional ten-year wait before the organism was cultured and its identity as a fungus established.[7-9] It was with remarkable foresight, therefore, that DeMonbreun[10] predicted that "the disease is more common than is generally supposed, possibly because . . . [it] may occur in a relatively mild or non-fatal form and not be recognized." This proved to be precisely true. Mild forms of histoplasmosis are now known to be commonplace, and recovery is not the exception but the rule. Yet amid incontestable proof of its prevalence and world-wide distribution the anomalous fact stands out that Panama, the site of Darling's discovery, has been conspicuously devoid of further evidence of the disease. Only in very recent years has any clue been furnished to the solution of this puzzling paradox.

Thus, although Darling's 3 cases were encountered within the space of eight months, it was forty years before another case was reported from Panama (1945), and that involved a dog.[11] Even so, there is reason to believe that the dearth of histoplasmosis in Panama is more apparent than real. Tucker,[12-15] for example, conducted elaborate skin-testing surveys indicating a high sensitivity to histoplasmin (39 per cent) among nonwhite Panamanian patients, the same group showing pulmonary calcifications as often as tuberculin-positive persons. In other words the situation was no different from that in other regions where histoplasmosis has been shown to be endemic. As Tucker stressed, these data did not in themselves prove the existence of histoplasmosis in Panama but certainly suggested that a continued search might prove productive.[14] Shortly after completion of his study his suspicions were borne out by the prompt discovery of the fourth case of histoplasmosis in Panama, a fatal case in a three-month-old infant.[13,16] Two other fatal cases have been alluded to but not reported.[17]

So far as nonfatal histoplasmosis is concerned, the first and only proved case from Panama has been recorded by Zimmerman.[17] Interestingly enough, the lesion, a solitary pulmonary granuloma, had been obtained in 1931 as an incidental finding at autopsy on a four-year-old Panamanian child who had died of malaria. With the use of special staining technics popularized by Puckett[18] and others[19-21] this "tuberculoma" was found to contain innumerable histoplasma that were invisible in routine tissue sections stained with hematoxylin and eosin. As Zimmerman pointed out, this case partially fills the long gap from 1906 to 1945, when no new cases of histoplasmosis had been reported from Panama.

Final unequivocal proof of the endemic nature of histoplasmosis in Panama has been provided by Ajello's[22] isolation of *Histoplasma capsulatum* from soil beneath a chicken roost in La Campana, Panama. By means of membrane filters[23] he was able to demonstrate typical macroconidia (so-called tuberculate chlamydospores) in the same specimen of soil. I am not surprised, therefore, at finding a fatal case of histoplasmosis contracted in Panama. What is remarkable is that this is the first case of disseminated histoplasmosis in an adult reported from Panama since Darling's classic studies fifty years ago.

Case Report

J.T.H., a 29-year-old Navy enlisted man, was admitted to the United States Naval Hospital, Bethesda, Maryland, on July 23, 1955, in transfer from the Panama Canal Zone, where he had been stationed for the preceding 20 months. He had been in apparent good health until late May, 1955, when right-sided pleuritic chest pain unaccompanied by cough or expectoration had developed. Subsequently, the onset of headache, vomiting, chills and fever prompted his admission on June 13 to Gorgas Hospital, Ancon, Panama Canal Zone. Physical examination was negative on that admission. Except for evidence of anemia, laboratory studies were within normal limits. Treatment was strictly empirical, consisting of multiple blood transfusions, penicillin, streptomycin and 250 mg. of cortisone daily. On the 5th hospital day a roentgenogram was reported as showing a small density at the right base (Fig. 1). Because of a persistent febrile course with daily temperature elevations to 105°F. he was transferred to the United States Naval Hospital, Bethesda, Maryland.

The past history was of questionable significance. Two years earlier (in July, 1953) he had become ill, manifesting a purpuric rash over the lower extremities, hematuria and bleeding gums. A tourniquet test produced a marked petechial rash within 4 minutes. The bleeding time was longer than 15 minutes, and the coagulation time was 2½ minutes. The peripheral platelet count was consistently below 20,000. The remainder of the laboratory work was normal. The administration of ACTH was followed by progressive improvement in capillary fragility but no increase in platelet count. Splenectomy resulted in an apparently complete recovery, whereupon the patient was ordered to the United States Naval Base, Rodman, Panama Canal Zone.

On admission to the United States Naval Hospital in Bethesda physical findings were unimpressive, although he was obviously quite ill. A roentgenogram of the chest (Fig. 2) showed a circumscribed nodular density in the right-lower-lung field, with an associated mediastinal mass in the region of the azygos lymph nodes. Initial examination of the blood disclosed a red-cell count of 2,100,000, with a hemoglobin of 8.6 gm. per 100 ml. and a hematocrit of 28 mm., and a white-cell count of 9200, with a differential count that was normal except for a predominance of band forms; a platelet count was 260,000 per cubic millimeter. Urinalysis was negative, as were malaria smears, urinary porphyrins and an L.E.-cell preparation. Bone-marrow aspiration was reported as follows:

> A granulocytic series shows normal maturation but marked toxicity. Erythrocytic series is increased, with

the majority of cells in the meta-rubricytic stage. Stippled cells and Howell–Jolly bodies are seen. Megakaryocytes but no marrow units are found.

Tuberculin and fungal skin tests were not done.

Cortisone, blood transfusions, penicillin and streptomycin were continued. ACTH, 40 units intravenously a day, was started. Chlortetracycline and later erythromycin, in 2-gm. daily dosage, were later instituted, without apparent benefit. There were daily temperature elevations to 104°F. along with shaking chills. Large doses of meperidine and morphine were required to control bone and joint pain.

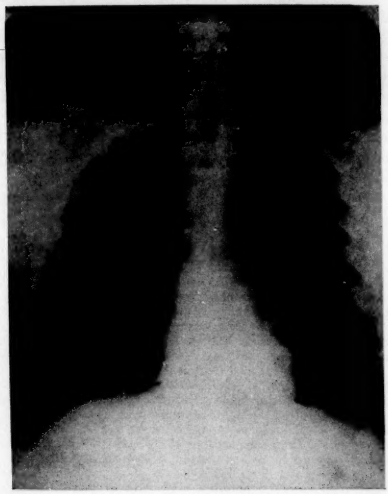

FIGURE 1. *Posteroanterior Roentgenogram of the Chest Taken at Gorgas Hospital at the Onset of the Illness, Showing a Small, Circumscribed Lesion in the Right Costophrenic Angle Interpreted As Localized Pneumonitis. There is also enlargement of the right hilar and azygos lymph nodes.*

Several days after admission the liver became palpable and grew progressively larger until it ultimately extended 10 cm. beneath the right costal margin. Bilateral pedal edema developed. All this, coupled with radiographic evidence of a mediastinal mass, raised the question of possible lymphoma. Nitrogen mustard (methyl bis [beta-chloroethyl] amine hydrochloride) therapy was instituted for a few days, but the patient grew worse, lapsed into coma and died on August 5.

At autopsy the only external feature of note was mild scleral icterus. The right lung weighed 1070, and the left 900 gm.; each appeared moderately congested. On cut surface a mucopurulent exudate could be expressed from the fine bronchioles. No note was made of any special findings in the right lower lobe. The right tracheobronchial and subcarinal lymph nodes were tremendously enlarged, having a pale, gelatinous appearance on sectioning (Fig. 3).

The liver was smooth and evenly enlarged, weighing 4700 gm. The capsule was purplish and presented mottled, grayish plaques. The liver parenchyma was reddish brown and showed a diffuse, yellowish-gray infiltration, as did the kidneys and adrenal glands. Other organs looked normal. There was conspicuous enlargement of the mesenteric lymph nodes, although not to the same extent as the tracheobronchial nodes.

Microscopical examination of the lungs, liver, lymph nodes, adrenal gland, kidney and bone marrow revealed a similar picture. Diffusely scattered throughout all these organs were focal collections of large cells whose cytoplasm contained many round, ruddy bodies, each with a clear surrounding halo typical of *H. capsulatum*. Extensive vacuolization and necrosis were present in all involved tissues along with an inflammatory reaction consisting mainly of lymphocytes, plasma cells and eosinophils, as well as scattered neutrophils. The bone marrow presented an almost complete absence of hematopoietic tissue, being replaced by a thin, fibrous network teeming with histoplasma. Multiple sections through other organs, including the brain, gave no evidence of involvement.

Tissue sections of spleen removed at operation 2 years earlier were obtained and restained. There was hyperplasia of germinal centers, along with extramedullary hematopoiesis. Associated lymph nodes were normal. Despite a concerted search of periodic-acid-Schiff-stained sections no histoplasma could be demonstrated. On the other hand, a review of the bone-marrow smear obtained 3 weeks before death disclosed myriads of organisms.

DISCUSSION

Although there is no absolute proof that this patient's illness was contracted in Panama, there is ample reason to believe that it was. For the twenty

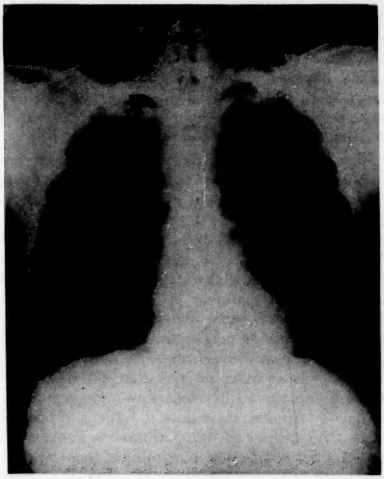

FIGURE 2. *Posteroanterior Roentgenogram Taken a Month after Figure 1, Showing an Increase in Density of the Peripheral Pulmonary Lesion, with a More Marked Increase in the Size of the Right Tracheobronchial Lymph Nodes.*

months before the onset of symptoms he had been stationed there, a period far exceeding the incubation period for *H. capsulatum* but not necessarily inconsistent with a latent form of the disease going on to delayed dissemination. Since hypersplenism is not rare in fatal histoplasmosis, having led on more than one occasion to misguided splenectomy,[24-28] it is natural to suspect in this case some relation between the

previous splenectomy and the eventual outcome. However, close retrospective scrutiny suggests such a suspicion to be unfounded, since no histoplasma could be demonstrated in the spleen in either Gridley or periodic-acid-Schiff-stained tissue sections, methods whereby organisms can ordinarily be demonstrated even in burnt-out splenic foci.[29] Moreover, the roentgenographic findings indicate a portal of entry via the lungs, which in earlier x-ray films had always been free of disease. Therefore, it seems illogical to think that the patient incurred the disease before reaching Panama.

To pursue the pathogenesis of this case farther, one would suspect from the radiographic appearance of the pulmonary lesion, with its tremendously enlarged

FIGURE 3. *Gross Specimen at Autopsy, Demonstrating the Tremendously Enlarged Tracheobronchial Lymph Nodes. These were teeming with histoplasma. The parenchymal component was apparently overlooked at autopsy.*

regional lymph nodes (Fig. 2), that this represents a type of disease analogous to the primary complex seen in pulmonary tuberculosis. Actually, for histoplasmosis to produce a lesion like this is known to be fairly common, but for fatal dissemination to ensue must be extremely rare, only a few such cases having been recorded.[30-32] Instead, primary histoplasmic infections almost invariably remain a localized and presumably innocuous process.[33] Nevertheless, the higher number of positive cultures obtained from apparently quiescent hilar and mediastinal lymph nodes of animals[34,35] has established the viability of these organisms and indicates a need for increased awareness of possible dissemination from just such an endogenous focus. In the present case, of course, there is no reason to suspect reactivation, since the pulmonary lesion appeared fresh and dissemination was undoubtedly immediate rather than delayed.

After reconstruction of the evolution and course of the disease, it is regrettable that the diagnosis could not have been made before death, especially when many histoplasma could be seen in a post-mortem reexamination of the bone-marrow aspirate obtained earlier. Certainly, in any case of unexplained fever and anemia accompanied by hepatic, pulmonary and lymphatic involvement, one should at least think of histoplasmosis as a possible cause. Ever since Darling's day reference is continually made to the similarity between histoplasmosis and leishmaniasis. In fact, the first case of histoplasmosis ever seen in this country (Children's Hospital, Washington, D. C., 1922) was initially misdiagnosed as kala-azar and reported as such,[36,37] and its true etiology not established until tissue sections were reviewed in 1941.[38,39] From a practical standpoint, however, the more common misdiagnosis in this country appears to be tuberculosis or, as in this case, lymphoma.

Even if the diagnosis had been established before death the outcome could hardly have been averted, for there is as yet no effective therapeutic agent. Perhaps the most promising drug to date is nystatin,[40-42] but in the light of periodic premature displays of enthusiasm for other agents still of questionable effectiveness (for example, the diamidines,[38,43,44] ethyl vanillate,[45-48] actidione,[49] quinacrine[50,51] and MRD-112[52-55]), special care should be taken lest every spontaneous remission be deemed a therapeutic triumph.

Here, at least, another unanswered question remains. Throughout most of his hospital stay at both Gorgas and Bethesda Naval hospitals the patient had been maintained on substantial doses of steroids. How much, if any, did this contribute to the dissemination and speedy termination of this case? In 1953 Shull[56] mentioned observations on 3 cases in human beings at Vanderbilt University School of Medicine suggesting that steroids might actually be harmful. In the same year a case of rapidly fatal histoplasmosis complicating a case of cortisone-treated exfoliative dermatitis was reported.[57] There seemed little doubt after experiments by the Ohio State group[58] that cortisone-treated dogs manifested fatal histoplasmosis soon after tracheal inoculation of mycelia, whereas untreated dogs did not. More recently, a case has been cited in which cortisone was thought to have contributed considerably to the clearing of acute pulmonary histoplasmosis, although possibly contributing to subsequent dissemination.[53] The same group, after investigating the effect of cortisone on histoplasmosis in the guinea pig, concluded that even though there was no appreciable

difference in mortality or morbidity rates of infected animals whether treated or untreated with cortisone, there appeared to be evidence of wider dissemination in animals receiving cortisone.[59] However, in a comparable study by Baum, Adriano and Schwarz[60] no such correlation was detectable. Moreover, the apparently deleterious effect of combined cortisone and x-ray therapy upon several other mycoses in animals[61,62] seems to be related to dosages far exceeding human therapeutic levels. In a recent review of histoplasmosis several cases were cited in which a "runaway spread" followed misguided cortisone administration,[32] prompting the authors to give a warning about the indiscriminate use of steroids in areas endemic for histoplasmosis. In the same vein others have commented that in a region where histoplasma is endemic, the prolonged use of cortisone in patients with sarcoidosis who do not have immunity to histoplasmosis may result in an increase of coexisting histoplasmosis and sarcoidosis.[59]

Although the present case was unquestionably fulminating, this is hardly unusual in cases of disseminated histoplasmosis untreated by steroids. Moreover, the prolonged administration of steroids to patients with histoplasmic Addison's disease does not seem to influence unduly the progress of the disease.[63] Of course, inferences drawn from such cases are not necessarily significant considering that the amount of circulating steroids is probably not excessive but in the range of normal. At any rate, any blame of cortisone or ACTH in this particular case seems unfounded, the clinical course and outcome being quite representative of the acute disseminated form of the disease.

Summary

The first adult case of disseminated histoplasmosis to be reported from Panama since Darling's classic studies fifty years ago is described. In the light of this and other recent developments one suspects that Panama is no different from other endemic areas where the true prevalence of the disease was, and still is, long gaining recognition.

The more interesting aspects of the case are discussed with special attention to its apparent evolution from a small primary-complex type of pulmonary histoplasmosis — a process now known to be almost invariably benign and inconsequential, instead of fatal as in this case.

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SCLERODERMA (PROGRESSIVE SYSTEMIC SCLEROSIS) ASSOCIATED WITH CANCER OF THE LUNG*

Brief Review and Report of a Case

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WESTFIELD, MASSACHUSETTS

As early as 1891 Dinkler[1] pointed out that scleroderma is a systemic disease that may affect the connective tissue of many organs. Therefore, a more appropriate name would be, "progressive systemic sclerosis," as proposed by Goetz.[2] This name, however, has not been generally adopted.

FIGURE 1. *Appearance of the Patient, Showing the Contracted Mouth and Tight, Glossy Skin on the Hands.*

The following case is considered to be of particular interest because of the development of cancer of the lung in association with scleroderma.

FIGURE 2. *Roentgenogram, Showing Marked Atrophy and Absorption of the Phalanges and Distal Ends of Both Ulnas, with Calcified Plaques in the Soft Tissues (Calcinosis).*

CASE REPORT

J.Z., a 31-year-old woman, had a chest film taken in a community x-ray survey in November, 1951, that showed fine reticular strands in both lungs. For this reason she

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was referred to the outpatient department of the Westfield State Sanatorium, where she was observed periodically until her death.

Ten years previously, pain and swelling of the small joints of both hands, wrists and feet had developed. Later,

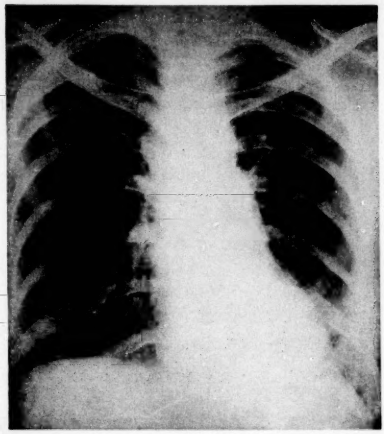

FIGURE 3. *Roentgenogram of the Chest, Taken on December 14, 1951.*

the pain and swelling gradually disappeared, and deformity and stiffness of the fingers and toes occurred. About 5 years before admission pain started in the mandibular joints, and

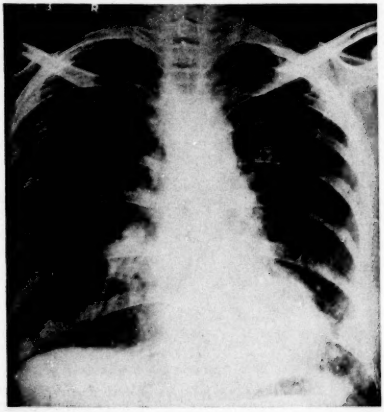

FIGURE 4. *Roentgenogram of the Chest, Taken on June 2, 1952.*

she noticed that the skin on her face, neck and arms was becoming thick and hard. An ulcer on the left external malleolus that healed slowly developed. Other complaints were dyspnea on exertion and difficulty in swallowing. Examination showed gross deformity of both hands and feet. The fingers were tapered and variously contracted. Both little fingers were short and tapered, and the distal parts loose. The skin on both hands was firm, pale and waxy in appearance, and bound down on bony prominences (Fig. 1). There were ulcers on several knuckles, and scars on others. The skin on both forearms, and around the elbows, was dry, thick, leathery and irregularly pigmented. This thick skin, which appeared bound down to the atrophic muscles and contracted flexor tendons, limited extension of both elbows to 150°. The skin on the face and neck was similarly affected. The circumoral skin was firm and inelastic, allowing very little motion of the atrophic lips (Fig. 1). Red, telangiectatic spots were scattered on the face. The skin from the clavicles down to the ankles was not noticeably affected.

The heart rate was irregular at the 1st examination only. An electrocardiogram at a later date was normal. The lungs were normal on auscultation.

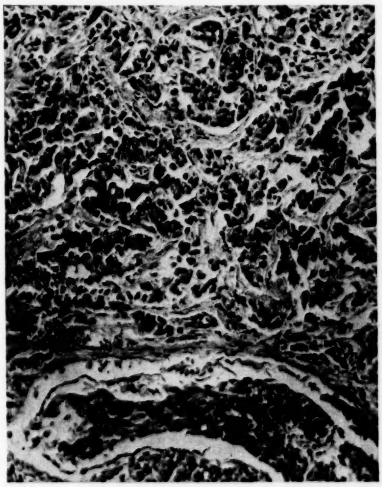

FIGURE 5. *Photomicrograph, Showing the Cellular, Undifferentiated Adenocarcinoma.*

X-ray examination of the hands, wrists and feet showed marked trophic changes with absorption of bone and calcinosis around the wrists (Fig. 2). Other bones, including the spine, demonstrated no abnormality.

Barium-swallow study showed a tortuous esophagus, with alternating areas of dilatation and nondistensible constriction. Passage of the barium was not significantly delayed.

Biopsy of skin from the right forearm revealed marked hyaline collagenization of the subcutaneous tissue and flattening of the papillae of the epidermis consistent with scleroderma. A roentgenogram of the chest, taken in December, is shown in Figure 3.

On April 22, 1952, treatment with cortisone, 150 mg. daily during the 1st month and 100 mg. daily thereafter, was started. Breathing and swallowing improved; there was increased use of the hands, and she was again able to do some work. The skin on the forearms seemed somewhat softer, and motion of the elbows freer. During the next 5 months she gained 4.1 kg. (9 pounds) in weight. A hilar mass became evident in June (Fig. 4). In December, she noticed increasing weakness and dyspnea.

On February 7, 1953, she was admitted to the Westfield State Sanatorium in respiratory failure, which led to death within 24 hours.

At autopsy the lower lobe of the right lung was almost entirely replaced by a nodular, firm tumor mass. Several other small tumor nodules were found in the upper and middle lobes. The tumor was mainly located around the larger bronchi. There was diffuse fibrosis throughout the left lung and several cysts at the base. Many round tumor nodules were found in the liver. The largest ones were 5 by 6 cm. in diameter. Furthermore, metastases were found in the hilar, mesenteric and para-aortic lymph nodes, adrenal glands and vertebral bone marrow.

On microscopical examination the lung tumor showed a quite cellular, undifferentiated bronchogenic adenocarcinoma (Fig. 5). In the more compact areas the tumor cells were uniform and lying in sheets, with a tendency to form glandular structures (Fig. 6). There was a small amount of fibrous stroma. Many mitotic figures were seen throughout the section. In several areas the tumor showed squamous metaplasia (Fig. 7). In the areas less affected — or not affected — by the tumor the parenchyma showed a striking increase in connective tissue and scattered foci of calcification and ossification.

The tumor nodules in the liver arose from the periportal connective tissue and were considered to be metastatic from the lung tumor.

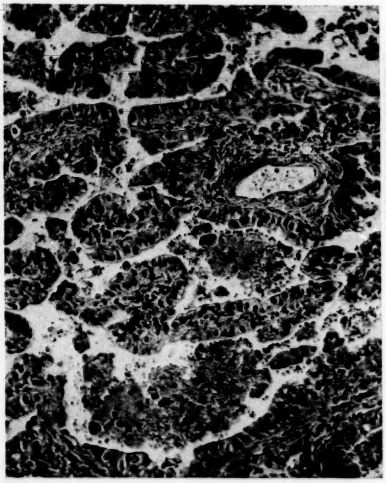

FIGURE 6. *Photomicrograph, Showing Uniform Tumor Cells in Sheets, with a Tendency to Form Glandular Structures.*

Microscopical examination of the esophagus and the stomach showed the mucosa to be somewhat thickened and edematous in some areas, but thin and atrophic in others. There was marked fibrosis throughout the submucosa of both organs. Connective tissue was also considerably increased in the muscular layers, and several muscle bundles were homogeneous and dark-pink stained and had lost their nuclei.

DISCUSSION

When this patient first came under our observation, the x-ray film of the chest showed the characteristic findings of diffuse interstitial fibrosis. She had already noticed moderate dyspnea on exertion for several years, undoubtedly because of interference with the diffusion of gases across the fibrous alveolar membrane. Ventilatory studies could not be performed because of the extensive scarring of the circumoral skin, which made it impossible for her to close her mouth on a mouthpiece.

Symptomatically, she improved greatly on cortisone therapy. Similar improvement has previously been reported in this disease.[3,4] Most authors have not

FIGURE 7. *Photomicrograph, Showing Squamous-Cell Metaplasia.*

seen any improvement from cortisone or any other treatment, and some have observed that ACTH induced hypertension and cardiac arrhythmias.[4,5]

Of primary interest in this case, however, is the development of cancer of the lung. In November and December, 1951, ten years after the onset of the illness, the diffuse fibrosis in the chest films was certainly no more extensive in the right lower lobe than elsewhere in the lungs, and there was no evidence of a hilar mass or bronchial obstruction (Fig. 3). In a period of two months (April and May, 1952) a mass in the right hilus became visible on the x-ray film (Fig. 4); incidentally, this occurred six weeks after treatment with cortisone was started. In spite of rapid extension of the disease in the right lower lobe the patient felt better and gained weight until six or seven weeks before death. This improvement can be attributed to the cortisone treatment.

The occurrence of cancer of the lung in a thirty-two-year-old woman is very rare. Therefore, one will wonder whether the scleroderma, a proliferative connective-tissue disease, is a precancerous lesion. The

presence of so much squamous-cell metaplasia may be a factor in the development of frank carcinoma.

In 1953 Zatuchni et al.[6] reported 3 cases of alveolar-cell carcinoma in patients with scleroderma. Their patients were forty-five, sixty-five and sixty-five years of age. In their search through the literature of scleroderma, they found no mention of its association with lung cancer.

The high frequency of cancer associated with dermatomyositis, another collagen disease closely related to scleroderma, has frequently been reported. Curtis et al.,[7] reviewing the literature on that disease in 1952, mentioned the finding of 27 such cases. To this they added 8 cases of cancers in a group of 45 cases of dermatomyositis observed at their hospital. They also stated that "several instances of neoplasms were found associated with scleroderma and lupus erythematosus." Even though dermatomyositis preceded the diagnosis of cancer in all their cases, on the average by eighteen and six-tenths months, they suggested that "perhaps the catabolic products of the neoplasm act as an allergen or toxin and serve as the trigger mechanism in causing the many changes that occur in this rather protean disease." The same theory has been advanced by others. The chief support for this theory is the fact that in several of their cases, the dermatomyositis improved with treatment of the neoplasm. A similar experience has been reported by others.

In the case presented above, the scleroderma had unquestionably existed for ten years before any signs of the rapidly growing lung cancer.

Summary and Conclusions

An extensive case of scleroderma in a thirty-two-year-old woman and the development of fatal cancer of the lung is reported.

The literature regarding the association of collagen diseases and malignant tumors is reviewed.

Although there is no uniformity in the type of tumors associated with the collagen diseases, they seem to occur more frequently than in other people of the same age. Therefore, the coexistence or a future development of a malignant tumor should always be considered in this group of patients.

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POLYNEURITIS IN SYSTEMIC LUPUS ERYTHEMATOSUS*

Review of the Literature and Report of a Case

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THE occurrence of neurologic symptoms and signs in the course of systemic lupus erythematosus is well known, but the majority of these are the result of involvement of the central nervous system. Only a few well studied cases of associated polyneuritis have been reported.[1,2] The incidental finding of peripheral mononeuritis, usually preterminally, has been recorded in a few autopsied cases without any report of the autopsy protocol of the isolated clinical findings.[3,4]

Sedgwick and Von Hagen[5] described the occurrence of polyneuritis in a case of systemic lupus erythematosus, but the data presented are insufficient to support the diagnosis. A second case of polyneuritis presumably associated with connective-tissue disease is reported by Richter,[6] but neither systemic lupus erythematosus nor periarteritis nodosa could be diagnosed with certainty by the author. Finally, there is the well documented case of polyneuritis occurring with systemic lupus erythematosus reported by Heptinstall and Sowry.[1]

It is the purpose of this paper to present a well studied case of systemic lupus erythematosus with prominent signs and symptoms of involvement of the peripheral as well as the central nervous system, and to compare it with similar cases reported in the literature.

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Case Report

J. M., an 18-year-old girl, was first admitted to the Neurological Institute on November 11, 1953, with the chief complaint of blurred vision of several days' duration. She had been in good health until the previous July, when soreness of the throat and feverishness developed, subsiding after

1 week without any specific therapy. In August she noted easy fatigability and migratory arthralgias involving the ankles, wrists and fingers. At that time the erythrocyte sedimentation rate was 45 mm. per hour (Wintrobe method). She was treated with a total dose of 300 mg. of cortisone, which relieved the arthralgias, but the fatigability persisted during the next month in spite of bed rest. For several days during October she experienced anorexia, nausea and vomiting, which also subsided without specific therapy. On November 1 pain and swelling over the left upper alveolar region and a temperature of 101°F. developed. This persisted for 10 days, during which she was treated by 3 injections of penicillin and removal of 1 tooth. At about the same time as the onset of fever, she had intermittent diplopia, which became constant after a few days and was accompanied by blurring of vision. In the month before admission she lost 10 kg. (22 pounds) in weight.

Physical examination showed an alert, well developed girl in no acute distress. The temperature, pulse, respirations and blood pressure were within normal limits. There was a slight malar flush, 1 enlarged anterior cervical lymph node and a Grade 1 apical systolic murmur. The remainder of the general physical examination was within normal limits. On neurologic examination the gait was noted to be wide based and ataxic, and there was generalized moderate to minimal weakness in all extremities. Except for depressed ankle jerks, the tendon and superficial reflexes were all normal. A slight terminal tremor was noted bilaterally in the finger-nose and heel-shin tests. Sensory examination was within normal limits. There were papilledema (5 diopters) bilaterally, peripapillary hemorrhages and numerous small areas of exudate and edema extending to the right fovea and temporal to the left fovea. The blind spots were grossly enlarged, and there was a suggestion of a central scotoma on the right. Visual acuity was 20/40 in the right eye, uncorrected. There was a paresis of the right abducens nerve, with nystagmus on right lateral gaze.

Examination of the blood disclosed a red-cell count of 4,200,000, with a hemoglobin of 12.8 gm. per 100 ml., and a white-cell count of 6500, with a normal differential. Platelets numbered 188,000. The sedimentation rate was 75 mm. per hour (Wintrobe method). The serum sodium was 133.8 milliequiv., the serum potassium 4.4 milliequiv., and the serum chlorides 101.0 milliequiv. per liter. The serum protein was 6.7 gm. per 100 ml., with an albumin of 3.9 gm. and a globulin of 2.8 gm. per 100 ml. Thymol turbidity was +++, and cephalin flocculation +++; bromsulfalein retention was 45 per cent after 5 minutes and 15 per cent after 30 minutes. The nonprotein nitrogen and fasting blood sugar were normal, and a Mazzini test and L.E.-cell preparation were negative. Repeated urinalyses during the 1st hospital admission showed albuminuria, cylindruria and microscopic hematuria. Lumbar puncture was performed, with an initial cerebrospinal-fluid pressure equivalent to 500 mm. of water; the fluid was clear and colorless, containing 7 white cells per cubic millimeter, with a protein of 270 mg. per 100 ml. X-ray examinations of the skull and chest were negative. An electrocardiogram was normal. An electroencephalogram showed a moderately disorganized record, with some slowing in the temporal areas bilaterally and additional slowing to 3 cycles per second with hyperventilation. No focal or paroxysmal features were otherwise noted.

On November 14 a ventriculogram was unsuccessfully attempted through occipitoparietal burr holes, without the ventricles being entered. A left-common-carotid arteriogram was negative with 1 anteroposterior seriogram.

On November 16 cortisone, 300 mg. a day, was started, and the dose gradually reduced until the patient was receiving 100 mg. a day by November 21. A repeated neurologic examination at this time revealed absence of tendon reflexes at the ankles, with absent vibration and position sensation at the ankles. The visual acuity was 20/100 in the left and 20/50 in the right eye, corrected, and the visual fields demonstrated only enlarged blind spots. There was some resolution of the papilledema and retinal hemorrhages. Laboratory data at this time included a hemoglobin of 10.4 gm. per 100 ml. and a sedimentation rate of 82 mm. per hour (Wintrobe method). Chronaxy studies revealed partial denervation of the muscles about the ankles in both lower extremities. No denervation was noted in the arms.

The patient continued to receive cortisone, 100 mg. a day, and in December the weakness of all extremities was more marked, with greater involvement distally. There was a minimal intention tremor in finger-nose and heel-shin tests, and all tendon reflexes were depressed except the ankle jerks, which were absent. There was generalized diminution of vibration and position sensation, more pronounced at the ankles than at the wrists. There was a stocking-and-glove type of hypesthesia to touch and pain. Repeated lumbar punctures showed cerebrospinal-fluid pressures varying between 200 and 280 mm. of water, normal cell counts, and protein values of 460 to 528 mg. per 100 ml. The serum electrolytes and renal-function tests continued within normal limits. Blood cultures were negative on several occasions, and the erythrocyte sedimentation rate remained elevated repeatedly. Tuberculin tests and heterophil-antibody agglutinations were negative. Repeated L.E.-cell preparations were negative, and blood counts were within normal limits. Albuminuria and microscopic hematuria occurred frequently. The dose of cortisone was reduced to 75 mg. a day on December 14, to 62.5 mg. a day on December 22 and 50 mg. a day on December 27. Chronaxy studies done a month after initial testing revealed extensive denervation of the muscles of the legs, forearm and hands. An electroencephalogram on December 7 showed no change from the previous record, and on December 23 there was improvement with only some generalized slowing.

In January, 1954, lumbar punctures revealed cerebrospinal-fluid pressures equivalent to 180 to 260 mm. of water, normal cells and protein contents of 345 to 535 mg. per 100 ml., with normal sugars. On January 2, when the dose of cortisone had been reduced to 25 mg. a day, there was a return of fever, with abdominal tenderness, nausea, vomiting, generalized glandular enlargement and a facial rash typical of lupus erythematosus. The cortisone was increased to 100 mg. a day. While receiving the dosage the patient occasionally had somatic delusions and was frequently depressed, with mood swings. Blood counts, serum proteins and electrolytes and the erythrocyte sedimentation rate continued to show no change from previous values. An electroencephalogram at this time disclosed more disorganization and slowing than on the previous recording. Neurologic examination revealed severe weakness of all extremities, with only traces of motion distally and fair to good power proximally. There was minimal atrophy of the distal muscles. Tendon reflexes were absent throughout. Position and vibration senses were absent below the ankles and wrists bilaterally, with hypesthesia in a glove-and-stocking distribution bilaterally. There were no other changes from the previous examinations. The dose of cortisone was gradually reduced to 75 mg. a day, and she was discharged from the hospital on February 11.

She was followed as an outpatient during the next 2 months, and there was gradual improvement in strength of the extremities so that she was able to walk a short distance with assistance; otherwise, there was no change in the neurologic status. With cortisone on alternating doses of 62.5 and 75 mg. a day, a fever developed, and the dose was raised on April 12 to 150 mg. and then reduced to 125 mg. a day after 1 week. On April 20 she had 2 generalized convulsive seizures, with turning of the eyes to the right as the only lateralizing signs, and she was readmitted to the hospital. The neurologic status was essentially unchanged, as were the spinal fluid, urine, blood chemical findings and blood counts except for a mild leukopenia (white-cell count of 4800). Dilantin, 0.3 gm. a day, was started and she was discharged from the hospital after a few days.

In the next month it became evident that a round face and hirsutism were developing. By May 1 she had become quite euphoric, with many somatic delusions, and ran an intermittent low-grade fever. In the next few days she became confused and disoriented and expressed paranoid ideas. She was readmitted to the hospital on May 3. Examination revealed a temperature of 102°F. and no other change in general or neurologic status except that she was disoriented, confused and negativistic, displayed irrational behavior and expressed numerous paranoid and somatic delusions. At times she seemed to be having active hallucinations. The only significant change in the laboratory data was an anemia (hemoglobin of 8.8 gm. per 100 ml. and red-cell count of 2,980,000). The dose of cortisone was reduced to 100 mg.

a day, and by May 8, with a further reduction to 75 mg. a day, she was quite clear mentally. An electroencephalogram during the acute psychosis showed predominant 4-6-cycles-per-second activity and was more disorganized than any previous recording. The L. E.-cell preparation was first positive on May 12. Two weeks after the clearing of the psychotic episode, the electroencephalogram indicated marked improvement though it was still abnormal, and she was discharged on June 5 on a dose of cortisone of 62.5 mg. a day. During the next 2 months there was a generalized improvement in motor power, and sluggish tendon reflexes could be elicited except at the ankles. Position and vibration senses were normal in the extremities.

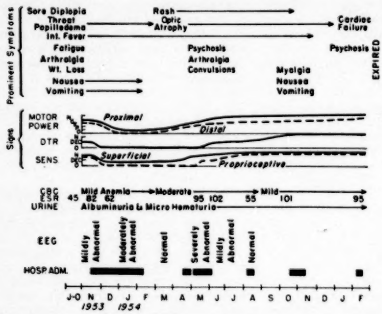

FIGURE 1. *Clinical Course of a Patient with Systemic Lupus Erythematosus, Showing Prominent Symptoms, Signs of Peripheral Neuropathy, Blood Counts, Erythrocyte Sedimentation Rates, Urinalyses and Electroencephalograms.*

Examination at the time of a 4-day hospital admission in August revealed a typical facial rash of lupus erythematosus, sluggish tendon reflexes throughout, except absent ones at the ankles, normal strength in the extremities proximally and moderate weakness distally. Laboratory data, including blood counts and blood chemical findings and studies of urine, liver function, spinal fluid and visual fields revealed no essential changes from the previous findings. An electroencephalogram was normal.

During the next 2 months there was gradual improvement in the peripheral neuropathy, the sensory examination now being completely normal though residual weakness was noted distally in the extremities. She began to complain of vague myalgias along with some low-grade fever, and she was admitted to the hospital on October 22. The general physical examination revealed no significant changes, whereas on neurologic examination the tendon reflexes were normal except for absent ones at the ankles. There was distal weakness and atrophy in the extremities. Otherwise, the examination was not remarkable. Laboratory data were unchanged on this admission except for a positive Mazzini test for the 1st time, normal blood counts and a 2d positive L.E.-cell preparation. She was discharged on November 14 on cortisone, 75 mg. a day. During the next month the dose was gradually increased to 100 mg. a day because of intermittent myalgias, arthralgias, fever and vomiting. Because of ankle edema she was also given Diamox and Mercuhydrin. By February, 1955, the dose had been raised to 112.5 mg. a day, and there were mood swings and bizarre bodily sensations. There was physical evidence of pleural and pericardial effusion (confirmed by x-ray examination), and she was readmitted to the hospital on February 7; there were no other essential changes in the physical and laboratory examination except for a hemoglobin of 8.0 gm. per 100 ml. and a hematocrit of 22 per cent. Dyspnea and pulmonary rales developed, and she died on February 13 in spite of digitalization and pericardial tap.

The clinical course, spinal-fluid pressure and protein and the total cortisone therapy are summarized in Figures 1-3.

On post-mortem examination bilateral thoracic and pericardial effusion was seen. There was increased eosinophilia of collagen under the pericardium, but the heart was otherwise not remarkable. Examination of the lungs revealed diffuse alveolar edema and numerous polymorphonuclear cells, which probably represented L. E. cells. In addition, there were numerous collections of hematoxylin bodies and pools of hematoxylin-staining material usually associated with lupus erythematosus.

On examination of the spleen there was marked pericentral-artery collagen deposition in concentric rings, a classic example of "onion skinning." The kidney showed numerous areas of old and recent necrosis along with the classic wire-loop changes in most glomeruli. In the ovaries there were many clumps of magenta-colored, amorphous material typical of the hematoxylin bodies considered pathognomonic of systemic lupus erythematosus and usually best seen in the ovary. There was mild atrophy of the adrenal cortex that was considered secondary to cortisone therapy.

There was also mild atrophy of the muscles, with focal areas of subacute inflammation and fibrinoid changes, some hematoxylin bodies and a few L.E. cells. The lymph nodes contained numerous areas of necrosis, hematoxylin bodies and L. E. cells.

The brain was pale, and the only gross defects were old puncture tracts in both occipital lobes secondary to ventriculography. The ventricles, meninges, cerebellum, brain stem and spinal cord appeared grossly normal, and sections at various levels revealed no gross abnormality of the parenchyma.

In microscopical sections there was a mild diffuse loss of nerve cells in the cortex. Acute inflammatory and necrotizing changes were found in the walls and in the substance of the brain and spinal cord. These were frequently thrombosed, with associated focal areas of necrosis in the brain and spinal cord. There was also a questionable degree of subacute and chronic changes in the vessels of the central nervous system, with thickening of the intima and narrowing of the lumen. Pink, amorphous material was present in the media of many arteries of the central nervous system.

The brachial plexus and the sciatic and femoral nerves were examined bilaterally. Most of the individual nerve fibers were separated by an accumulation of interstitial amorphous material. The endoneurium and perineurium had a loose reticular appearance. The epineurium had likewise become displaced from the nerve bundles by similar, grayish-blue amorphous material. With myelin-sheath stains of the nerves there was a spreading apart of the individual myelinated fibers by the accumulation of amorphous material. In addition there was swelling of myelin segments in some areas and a definite reduction in the number of myelin sheaths in others. In the axonal stain a definite reduction in the number of axons was seen, and those remaining were widely separated by amorphous material. This material did not stain with silver stain or mucicarmine stain. It did stain faintly blue with hematoxylin and was considered related to the hematoxylin bodies observed in blood vessels.

DISCUSSION

The clinical picture in this case leaves little question about the diagnosis of systemic lupus erythematosus. The symptoms of fever, butterfly skin lesion, photosensitivity, arthralgia, myalgia, weight loss, cardiac failure, generalized lymph-node enlargement, nausea, vomiting, convulsions and psychosis are all fairly frequent in systemic lupus erythematosus and need little additional comment here. Furthermore, this patient had the laboratory findings of anemia, hematuria, albuminuria, impaired liver function, positive blood serologic tests and L.E. cells as final confirmatory evidence for the diagnosis of systemic lupus erythematosus. At autopsy the typical pathological findings were present in the lungs, spleen, gall bladder,

kidneys, ovaries, muscles, lymph nodes, leptomeninges and peripheral nerves.

Bilateral papilledema with hemorrhages and choroidal exudates were observed in this case. These findings are not unusual in systemic lupus erythematosus. Maumenee[7] noted similar changes in 5 cases with clinical or histologic evidence of papilledema. It is interesting, however, that the 2 patients in whom lumbar punctures were performed had completely normal spinal fluids. In 105 cases reported by Harvey et al.[8] there were 2 with papilledema, 11 with retinal hemorrhages and 6 with exudates.

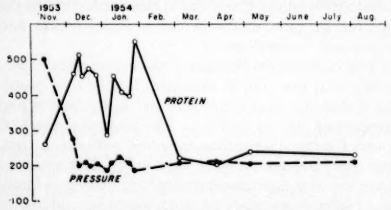

FIGURE 2. *Spinal-Fluid Pressure (Mm. of Water) and Total Protein (Mg. per 100 Ml.) during the Entire Course of the Illness.*

The occurrence of neurologic symptoms and signs early in the course of systemic lupus erythematosus has occasionally been noted. In 3 cases reported by Siekert and Clark[9] the initial complaints were chorea, hemiplegia, paraplegia, diplopia, dizziness and paresthesias. In the present case, though there were other characteristic symptoms of systemic lupus erythematosus earlier, the striking manifestations that led to hospitalization were the result of involvement of the nervous system.

The initial neurologic complaints in this case were related to involvement of both the central and peripheral nervous system. Initially, the increased intracranial pressure, as evidenced by papilledema, enlargement of the blind spots and abducens paralysis, led to the tentative diagnosis of an intracranial neoplasm. Ventriculography was attempted, but was unsuccessful. Some evidence of polyneuropathy with generalized weakness and depressed ankle tendon reflexes was present, however, before ventriculography was attempted. Loss of vibration sense and position sense at the ankles and denervation of muscles in the legs by chronaxy studies were noted in the next few days. The presence of denervation suggests that the neuropathy had existed for at least several weeks before hospitalization.

Though papilledema with hemorrhages and exudates is not unusual in systemic lupus erythematosus, the spinal-fluid pressure and chemical constituents were normal in many of the reported cases. This patient had repeated lumbar punctures with pressures ranging from 600 mm. of water in the initial stages to 180 mm. in the late course of the disease. The spinal-fluid protein initially was 270 mg. and increased to 535 mg. per 100 ml. In general the spinal-fluid protein in this case seemed to increase as the pressure decreased. Lumbar punctures were performed in 30 of the 138 cases studied by Harvey et al.[8] Only 1 of these patients had increased pressure, but the protein content was elevated in 7. Increased spinal-fluid protein was also noted in 1 case by Plotz, Blunt and Ragan.[10]

Psychotic episodes similar to those in the case presented above are reported in approximately 30 per cent of patients with systemic lupus erythematosus and are probably the most common cerebral complication.[11] These episodes are usually characterized by confusion, disorientation, delusions and hallucinations.[12-14] Psychotic manifestations may occur in systemic lupus erythematosus regardless of ACTH or cortisone therapy. In this patient, however, the mental changes developed about a week after an increase

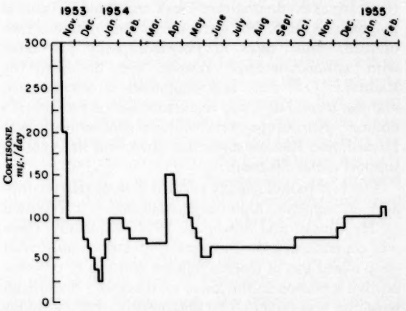

FIGURE 3. *Cortisone Therapy (Mg. a Day) during the Course of the Illness.*

in the dosage of cortisone on two occasions and cleared when the dosage was reduced. Since psychotic episodes have been reported in patients on steroid therapy in the absence of systemic lupus erythematosus,[15] it is possible that such episodes were related in part, at least, to the therapy given in the present case, for they cleared on reduction in the dosage. It was also noted that the electroencephalogram at this time was more abnormal than at any other time and became less abnormal as the patient showed clinical improvement.

Convulsive seizures, which occur in 25 to 30 per cent of cases of systemic lupus erythematosus, are second to psychotic episodes as the most common neurologic complication.[11] The electroencephalographic abnormality is one of diffuse disorganization, usually with slowing to 3-7 cycles per second of moderately high-voltage or less often 6-8 cycles per second of medium-voltage activity. The electroen-

cephalographic changes usually parallel clinical changes, as in this case.[16]

The most unusual feature was the onset of polyneuropathy. In a review of the neurologic manifestations of all forms of collagen diseases Glaser[11] states that the peripheral nerves are involved in systemic lupus erythematosus. From a review of the reported cases, it seems that the rate of occurrence is probably about 1 or 2 per cent. Isolated cases of an apparent mononeuropathy have been described, but this was usually found preterminally.[3,4] In the case presented by Sedgwick and Von Hagen[5] the diagnosis of systemic lupus erythematosus was made on a skin biopsy with little else clinically to suggest diffuse collagen disease. The clinical data given by them for support of the diagnosis of "polyneuronitis" included glove hypesthesia of the arms and spotty hypesthesia of the legs, slight weakness of the hand grips, bilateral Babinski reflexes and a spinal-fluid protein of 240 mg. per 100 ml. There were no changes in the tendon reflexes. In a review of 100 consecutive cases of systemic lupus erythematosus, Clark and Bailey[2] reported polyneuritis in 3, but gave no further details. Two unquestionable cases of polyneuropathy associated with connective-tissue disease are described by Richter.[6] One case was diagnosed as scleroderma, and the second as lupus erythematosus or periarteritis nodosa. No autopsy or definitive studies were performed, and Richter states that there was little else to support either diagnosis.

The first pathologically verified case of polyneuropathy in systemic lupus erythematosus was reported by Heptinstall and Sowry[1] in 1952. Clinically, there was generalized motor weakness, greater distally, with generalized loss of tendon reflexes and loss of proprioceptive sensation in the lower extremities. Superficial sensation was intact. The diagnosis of systemic lupus erythematosus was verified only at autopsy, and there is no discussion of the course of the polyneuropathy.

The clinical findings indicating polyneuropathy in their case were similar to those in the present case. Proprioceptive sensations were primarily involved in both cases. In the case reported above, cutaneous sensation was diminished in a glove-and-stocking distribution some weeks after the loss of proprioceptive sensation was noted; sensation remained impaired long after cutaneous sensation had returned. Also, the power in the extremities was lost gradually over a period of a month or more and advanced to complete paralysis of the distal muscles and paresis of the proximal muscles accompanied by areflexia. Strength then began to return gradually along with the tendon reflexes. By the time of death there was normal sensation and normal motor power proximally, with only slight paresis distally, and absent ankle jerks as evidence of the neuropathy.

In the case reported by Heptinstall and Sowry[1] the changes in the peripheral nerves were confined to an abnormality of vessels of the epineurium, loss of some nerve fibers and increase in amount of endoneurium. The blood vessels showed obliteration of the lumen, with recanalization and thickening of the intima. The pathological changes in the peripheral nerves in the present case included a permeation of the endoneurium and perineurium by amorphous material separating the connective-tissue fibers of the involved coverings. This material showed none of the features of collagen degeneration, and the pathologist believed that it might be related to the hematoxylin bodies observed in the walls of the blood vessels. On myelin-sheath stain there was some reduction in myelin sheaths, and in Bodian and phosphotungstic acid hematoxylin stains there was a clear reduction in the number of nerve fibers in the brachial plexus and sciatic and femoral nerves.

The pathological changes in the nerves seem to correlate with the clinical findings. It might be postulated that the amorphous material in the nerves had compressed the nerve fibers. The proprioceptive and motor functions were most involved, with touch next, and pain and temperature very little. This seems to correlate with experimental data indicating that large-nerve-fiber types carrying proprioceptive and motor impulses are most susceptible to damage by compression.

Summary and Conclusions

A case of systemic lupus erythematosus, studied from the clinical and pathological points of view, is reported. The clinical picture was typical of systemic lupus erythematosus. Involvement of the nervous system was manifested by increased intracranial pressure, psychosis, convulsions and polyneuritis. The unusual feature was the severity and the widespread nature of the polyneuritis. Only 1 other pathologically studied case has been reported previously.

It is believed that the deposition of amorphous material, similar to hematoxylin bodies in the other tissues, produced a polyneuritis by compression of the nerve fibers.

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SPECIAL ARTICLE

THE RE-LEGALIZATION OF ABORTION IN SOVIET RUSSIA

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ON November 23, 1955, the Praesidium of the Supreme Soviet of the U.S.S.R. passed a decree repealing the prohibition on abortion that had been in force for almost two decades. This marked the third time that the Soviet Union changed its stand on the question of permitting or prohibiting abortion on other than "therapeutic" grounds in the thirty-nine years of its existence. In the light of this, it appears worth while briefly to review the policies of the Soviet government on this very important social and medical problem.

Soviet legislation on abortion falls into four distinct periods: 1917-1920, in which abortions were illegal, even on medical indications; 1920-1936, in which abortions were legal provided certain conditions were met; 1936-1955, in which abortions again were illegal, except on certain medical indications; and 1955 to the present, in which abortions are again legal.

REVOLUTION TO 1920

During the Czarist regime, abortions were illegal, no legislation permitting the operation to be performed, even on medical grounds. No legislation was introduced during the first three years of the Soviet regime, and apparently the prohibition remained legally in force during these years. These years were, of course, years of great social and political upheavals, of revolution and counter-revolution, civil war and foreign intervention, famine and epidemics. Although no statistics are available, it can be assumed that the abortion rate was high and was accompanied, correspondingly, by a high rate of complications, including a heavy mortality.[1] This led the regime, particularly the organs of health, to consider the legislation of abortion to reduce the harm caused by the illegal performance of the operation.

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1920 TO 1936

On November 18, 1920, a decree jointly issued by the Commissariats of Health and Justice legalized abortion. The decree was preceded by a commentary, as Soviet decrees usually are, setting forth the reasons for the measure. It began by stating that in the past decade the number of women resorting to the artificial termination of pregnancy had grown both in the West and in Russia. Furthermore, legislation attempted to combat this evil by punishing the woman and the physician. Such legislation not only was useless but also drove the operation underground and made the woman a victim of mercenary and often ignorant quacks who made a profession of the secret operation. As a result, "up to 50 per cent of such women are infected in the course of the operation, and up to 4 per cent of them die." The Workers' and Peasants' Government, the decree went on, was conscious of this serious evil to the community and combated it by propaganda against abortion among women. Furthermore, the Government was certain that by "working for socialism and by introducing [measures for] the protection of maternity and infancy on an extensive scale" this evil would gradually disappear. And yet, since "the moral survivals of the past and the difficult economic conditions of the present still compel many women to resort to this operation," the Commissariats of Health and Justice, anxious to protect the health of the women and considering that the method of repression in this field entirely failed to achieve this aim, decided as follows:

(1) To permit such operation to be made freely and without any charge in Soviet hospitals, where conditions are assured of minimizing the harm of the operation;
(2) To absolutely forbid anyone but a doctor to carry out this operation;
(3) Any nurse or midwife found guilty of making such an operation will be deprived of the right to practice, and tried by a People's Court;
(4) A doctor carrying out an abortion in his private practice with mercenary aims will be called to account by a People's Court.[2]

It is quite evident, from the text of the decree, that the regime legalized abortion only as a last resort to minimize the harm caused by the practice and considered it, at the time, a temporary measure. When social conditions improved, so went the reasoning, abortions would become unnecessary, and the problem would cease to exist. Thus, although the Health Commissariat made it possible for pregnant women to obtain the artificial termination of their pregnancy, it attempted to reduce the abortion rate by several measures. One was the dissemination of birth-control information and contraceptives carried through the so-called "Women's Consultation Centers."* Parallel to this, an effort was made to develop the necessary facilities (crèches, kindergartens and so forth) to help women care for children and thus to reduce the abortion rate. Finally, a campaign of education was started to explain that abortions, even when carried out under the best hospital conditions, still carry risk for the woman's health and to attempt to dissuade women from having such an operation performed.[4]

There were, of course, certain restrictions on abortions even under the law of 1920. As mentioned above, the operation had to be performed by a licensed surgeon. It must, furthermore, be the result of a surgical intervention and not of drugs. The patient must remain in bed for three full days in the place where she was operated on. She must not be allowed to work for two weeks after the operation. More important, however, was that an abortion for a first pregnancy (unless it seriously endangered the woman's health) must be strongly discouraged by the physician and, if at all possible, not performed. Indeed, doctors were urged to discourage, in any way they saw fit, the performance of the operation but could not refuse it unless the pregnancy had lasted for more than two and a half months. It was furthermore recommended that all such operations be performed in hospitals that had special abortion divisions (called *abortarium*). A private physician or anyone else performing an abortion resulting in death could be tried for manslaughter, but women performing abortions on themselves could not be prosecuted. Finally, doctors were urged "to discourage a woman from abortion if there were no social, economic, or medical reasons for it, and particularly if she had fewer than three children or had adequate means for supporting another child."[5]

At the First Ukrainian Conference of Gynecologists, held in Kiev in 1927 to discuss experience with abortion for "social" indications, doctors noted a significant increase in the number of abortions in towns and villages; they believed that the legalization of the operation had led to a decrease of secret abortions and subsequent diseases and deaths. They furthermore noted that the legalization of abortion had not led to a decrease in the natural growth of the population, but that the population should be warned of the harm caused by the operation. A solution to the problem was the use of harmless contraceptives, and it was resolved that more attention should be paid to anticonceptional devices.[6]

At the Conference, statistics were presented of the relation of all abortions initiated or completed in all Moscow clinics to the total number of births registered in Moscow for the years 1922-1926, and the proportion between artificial abortions initiated in the clinics and cases of miscarriages, probably due to secret abortion, in patients who entered a clinic to have an abortion completed. These figures are given in Table 1. These figures show that, over the years, the proportion of abortions to births increased, but that the rate of incompleted abortions (presumably secret) decreased from 46 per cent to 20 per cent. Over the five years examined, the absolute number of abortions increased 400 per cent. Other statistical data were presented at the conference. For example, at the Dostoyevsky Hospital in Moscow, in 1925, 2696 abortions were performed; nearly all women were between twenty-one and thirty years old. For half these women, this was the first abortion; for 38 per cent, it was either the second or the third. In 58.7 per cent the cause was material insecurity; in 8.6 per cent, it was an excessive number of children, and in only 7.2 per cent was it for medical reasons. Perforation of the womb occurred in 0.15 per cent of all cases.[6]

According to a statement made to Newsholme and Kingsbury,[7] when they visited the Soviet Union in 1932, the legalization of abortion was said to have saved the lives of 300,000 women in the twelve years between 1920 and 1932. The mortality was reported as less than 1 per cent (0.74) since 1920, with practically no fatal cases in Moscow, where the operation was performed under good hospital conditions and by skilled surgeons. The mortality rate was higher outside the capital.

Between 1922 and 1929 the number of induced abortions in proportion to spontaneous abortions was reported as having increased almost twelve times in Moscow (Table 2).

The years between 1921 and 1929 were years of relative prosperity, the result of Lenin's New Economic Policy, which re-established a measure of capitalism and free trade. At the end of the twenties, the Communist Party, under Stalin's direction, embarked on a massive program of industrialization and collectivization of agriculture. This program entailed a policy of enforced savings to accumulate capital, and widespread dislocation of populations from the land areas to the cities and industrial centers. Urban housing became extremely scarce, and families most often had to content themselves with one room, sharing bathing, toilet and cooking facilities with other families in the same apartment. In addition, the need

*Zhenskii Konsultatsii. These centers are usually attached to maternity homes and provide all-round outpatient medical care for mothers before and after the birth of the child.[3]

for manpower meant that more and more women were being drawn into the labor force or had to go to work to supplement the family budget. Under these circumstances, it is fairly safe to assume that the rate of abortions significantly increased above the figures of the twenties, although no statistics are available to me. In many cases managers of industry adopted the practice of not hiring pregnant women, because the factory would then have to pay them while they were confined and also for some time afterward.[9] This, of course, also contributed to a rise in the abortion rate.

It is a commonly accepted fact that industrialization, urbanization and the movement of populations to the cities lead in most countries, at least in the initial stage, to a decrease in the birth rate and that the Soviet Union cannot have escaped this phenomenon. Since, at the same time, abortions and birth-control information and devices were available, it must have become apparent to the authorities that the effect on the birth rate would, sooner or later, become alarming, particularly in view of the worsening international situation in the mid-thirties and the very real possibility of war. It had also become apparent to the regime that its family legislation (regarding divorce, alimony *and* abortion) encouraged what was called a "light-hearted attitude" toward family responsibilities, increased family instability and the number of children who grew up in a disorganized atmosphere without supervision or discipline. The human products of such an environment, it was reasoned, would hardly become the stable, hard-working and conscientious workers required for an industrialized society.

As a result, a draft law was formulated in 1936 on the subject of abortion, and the tightening of family responsibilities. The regime, in a rare moment of liberalism, invited the Soviet population to discuss the draft and to present suggestions. On the subject of abortions, the general feeling on the part of the population (and particularly women) was that under the conditions existing at that time, women should have a right to limit the number of children. The reason most often mentioned was, of course, the lack of adequate housing and the need for women to acquire an education and to work. The medical profession, at the same time, although accepting the *social* reasons for permitting abortions, continued to warn the population of the *medical* dangers of the operations. The following extracts from letters published in the Soviet press at the time give a flavor of the discussion:

[*Letter from a student*] ("I Object")

I have read in the press the draft law on the prohibition of abortion . . . and cannot remain silent on the matter.

There are thousands of women in the same position as myself. I am a student in my first year at the Second Moscow Medical Institute. My husband is also a student . . . at our Institute. Our scholarships jointly amount to 205 roubles. Neither he nor I have a room of our own. Next year we intend to apply for admission to a hostel, but I do not know whether our application will be granted. I love children and shall probably have some in four or five years. But can I have a child now? Having a child would mean leaving the Institute, lagging behind my husband, forgetting everything I have learnt and probably leaving Moscow because there is nowhere to live . . . I consider that the projected law is premature because the housing problem in our town is a painful one. Very often it is the lack of living quarters that is the reason behind an abortion. If the draft included an article assuring married couples, who are expecting a baby, of a room — that would be a different matter.

In five years' time when I am a doctor and have a job and a room I shall have children. But at the present I do not want and cannot undertake such a responsibility.[10]

TABLE 1. *Births and Artificial and Incompleted Abortions (Moscow, 1922-1926).**

YEAR	NO. OF BIRTHS	TOTAL ABORTIONS	ARTIFICIAL ABORTIONS		INCOMPLETE ABORTIONS	PERCENTAGE OF ALL ABORTIONS TO BIRTHS	PERCENTAGE OF ARTIFICIAL ABORTIONS TO BIRTHS
			NUMBER	PERCENTAGE			
1922	35,320	7,969	4,245	53.27	3,724	22.56	12.0
1923	48,852	9,062	3,829	42.14	5,233	19.16	8.65
1924	51,980	10,183	5,782	56.78	4,401	19.56	11.12
1925	57,537	18,071	15,261	84.45	2,810	31.41	26.54
1926	†	31,986	25,239	80.0	6,393	—	—

*Based on paper by Prof. M. G. Szerdukov, director of the Graverman Maternity Clinic, Moscow, on "Artificial Abortion As a Biological Trauma," as quoted by Schlesinger.[8]
†Not available.

A group of women collective farmers sent a letter to *Izvestiya* in which they proposed that a woman who was nursing a child and who again became pregnant should be allowed to have an abortion, and that other conditions (presumably *social* conditions) under which abortions would be permissible should be clearly stated so that doctors could not refuse a patient.[11]

In a letter to *Izvestiya* entitled "Abortions Cannot be Categorically Forbidden," "an engineer" wrote as follows:

I do not belong to the party; I am married and have a five-year-old child; I work as an engineer . . . I regard myself as a good citizen of the U.S.S.R. I cannot agree with the prohibition of abortions . . .

The prohibition of abortion means the compulsory birth of a child to a woman who does not want children . . . Where the parents produce a child of their own free will, all is well. But where a child comes into the family

against the will of the parents, a grim personal drama will be enacted which will undoubtedly lower the social value of the parents and leave a mark on the child . . .

To my mind any prohibition of abortion is bound to mutilate many a young life. Apart from this, the result of such a prohibition might be an increase in the death-rate from abortions because they will be then performed illegally. . . ."[12]

Professor K. Bogolepov, of Leningrad, however, was not favorably disposed toward abortions. He urged that the greatest care be taken in reaching a decision on the subject, stating that: "Abortions will become obsolete by themselves when knowledge of human anatomy spreads, when methods of birth-control are more widely used and last — but not least — when housing conditions are improved."[13]

Professor M. Malinovsky, on the other hand, pointed out the specific health hazards of abortion. In a letter, entitled, appropriately enough, "Do Not Underrate the Evil," he wrote:

. . . People do not see or do not want to see the dangers inherent in abortion. The fact that the operation goes unpunished and is relatively safe has created an illusion of the complete harmlessness of the operation. It is our duty to dispel this misconception.

Performing an abortion is an operation undoubtedly involving great risks. There are few operations so dangerous as the cleaning out of the womb during pregnancy. Under the best of conditions and in the hands of the most experienced specialist the operation still has a "normal" percentage of fatal cases . . . The operation is performed in the dark and with instruments which, so far as their effect on so tender an organ as the womb is concerned, remind one of a crowbar . . . Apart from the direct danger which the operation has for women (penetration of the womb, heavy hemorrhage) i.e. dangers threatening life, there are more remote dangers threatening a woman's health (catarrhs of the womb, sterility, pregnancy outside the womb, etc). Such are the implications of abortion, an operation which is dangerous to the female organism and a heavy responsibility for the doctor. That is why we oppose it . . ."[14]

Finally, a "research worker" admitted that abortions were harmful to health but argued that there were a number of circumstances in everyday life that made it a heavy burden to have a large family. In addition, shortages in nurseries, kindergartens, dining halls, housing and equipment made married life and the care of children a hard toil:

. . . We all want to be "working women." The tribe of "housewives" is dying out and should . . . become extinct . . . I think that a happy Soviet woman, assisted by the solicitude of the Party and government, will herself not want to evade the joys of motherhood.[15]

Although it is safe to infer that public opinion was against the absolute repeal of the abortion laws (at least until the living conditions, particularly housing, had improved) the regime passed legislation forbidding abortions.

1936 TO 1955

As in 1920 the decree prohibiting abortions was accompanied by a commentary. It started by asserting that the Revolution had laid the foundations for the abolition of all class exploitation, for the abolition of classes themselves and for the complete and final emancipation of women. In no country in the world, it furthermore asserted, did woman enjoy such complete equality in all spheres of life. Nowhere, it went on, did woman, as a mother and citizen who bore the great and responsible duty of giving birth and bringing up citizens, enjoy such respect and protection as in the U.S.S.R. The decree then went on to enumerate the reasons that had led the regime to permit

TABLE 2. *Induced versus Spontaneous Abortions (Moscow, 1922-1929).*

TYPE OF ABORTION	NO. OF CASES							
	1922	1923	1924	1925	1926	1927	1928	1929
Base for spontaneous abortions	100	100	100	100	100	100	100	100
Induced abortions	114	73	131	402	417	695	894	1,240

*Based on Newsholme & Kingsbury.[8]

abortions in 1920 and repeated the arguments advanced at that time. The population was further reminded that, in 1913, Lenin had written that class-conscious workers are "unquestionable enemies of neo-Malthusianism, this tendency for the philistine couple, pigeon-brained and selfish, who murmur fearfully: 'May God help us to keep our bodies and souls together; as for children it is best to be without them.' " Whereas Lenin rebelled against abortions as a social evil, he considered legislation banning abortions as clearly inadequate to combat them. Moreover, he was said to have pointed out that "under capitalist conditions these laws only reflect the 'hypocrisy of the ruling classes' " since they [laws] "do not heal the sores of capitalism but make them particularly malignant, particularly painful to the oppressed masses."

It is only under socialism, the decree then stated, that exploitation of man by man does not exist, woman is an equal member of society, the progressive improvement of the well-being of the workers constitutes a law of social development and "it is seriously possible to organize the struggle against abortions by prohibitive laws as well as by other means":

The abolition of capitalist exploitation in the USSR, the growth of the material well-being and the gigantic growth of the political and cultural level of the toilers make it possible to raise the question of a revision of the decision of . . . November 18, 1920.

Necessary material provision for women and their children, state aid to large families, the fullest development of the network of maternity homes, nurseries, kindergar-

tens, legislative establishment of the minimum sums which the father of a child must pay for its upkeep when husband and wife live apart, on the one hand, and the prohibition of abortions on the other, coupled with an increase in the penalty for the wilful nonpayment of alimony for the maintenance of the children . . . and the introduction of certain changes in the legislation on divorces for the purpose of combating a light-minded attitude toward the family and family obligations — such are the roads to be followed in order to solve this important problem affecting the entire population . . .

In connection with the above and taking into consideration certain remarks made by citizens during the discussion of the draft, the Central Executive Committee [of the Party] and the Council of Peoples' Commissars of the USSR *decide:*

I. On The Prohibition of Abortions

1. In view of the proven harm of abortions, to forbid the performance of abortions both in hospitals and special health institutions, and in the homes of doctors and private homes of pregnant women. The performance of abortion shall be allowed exclusively in those cases when the continuation of pregnancy endangers the life or threatens serious injury to the health of the pregnant woman and equally when a serious disease of the parents can be inherited and only under hospital and maternity home conditions.

2. For the performance of abortions outside a hospital or in a hospital under conditions violating the above provisions, the doctor performing the abortion shall be criminally punishable with imprisonment of one to two years, while for the performance of abortion under unsanitary conditions or by persons who have no special medical education a criminal penalty of no less than three years' imprisonment shall be fixed.

3. For compelling a woman to undergo an abortion, a criminal penalty of two years' imprisonment shall be fixed.

4. In relation to pregnant women undergoing an abortion in violation of the said prohibition, to establish as a criminal penalty a social reprimand, and in the event of a repetition of the violation of the law on the prohibition of abortions, a fine up to 300 roubles.

The other articles of the decrees bear on measures to increase material aid to women who give birth, the establishment of stipends for large families, the extension of the network of maternity homes, nurseries and kindergartens, and financial steps to implement the program.[16]

The medical indications for abortions were made available by the Commissariat of Health shortly thereafter. They were as follows:

1. Serious chronic organic diseases of heart and blood vessels; endocarditis with anatomical lesions of the valves of the heart; organic diseases of the valves of the heart and diseases of the heart muscles, leading to circulatory insufficiency (oedema, indurated liver, cyanosis, shortness of breath); permanent hypertension which has not been caused by pregnancy.
2. Chronic forms of inflammatory degenerative and sclerotic processes of the kidneys, impairing their functions.
3. Nephrolithiasis on both sides (based on X-ray evidence).
4. Open form of pulmonary tuberculosis and also closed tuberculous infections of lungs and pleura with chronic intoxication.
5. Tuberculosis of the urinary tract, peritoneum, intestines, bones, joints, and larynx.
6. Chronic diseases of the liver with manifest functional disturbances.
7. Graves' disease with manifest insufficiency of the heart and circulatory system or with other chronic intoxications.
8. Pernicious anemia (Biermer type) and pernicious anemia as a result of pregnancy.
9. Leukemia.
10. Patients suffering or having suffered from malignant tumors.
11. Epilepsy diagnosed in a medical institution.
12. Retinitis or neuritis of the optic nerve caused by pregnancy or by diseases of the peripheral vascular system.
13. Serious diseases of the cornea as a result of physical exhaustion or endocrine disorders caused by pregnancy (for instance: Hypopyonkeratitis, keratoconus).
14. Narrow pelvis with conjugata vera of 7.5 centimeters and less, considerable deformities of the pelvis of various origins, and also considerable scarifications of the vagina making childbirth through natural channels impossible.
15. Abortion is permitted if mother, father or one of the children have suffered or are suffering from one of the following hereditary diseases: haemophilia, idiocy, genuine epilepsy, severe forms of schizophrenia or manic depressive psychosis, which have been treated in hospitals; serious hereditary diseases of the eye leading to blindness; hereditary deafness and dumbness; hereditary progressive disease of the nervous system (progressive muscular atrophy, hereditary ataxia).

Contra Indications for the artificial interruption of pregnancy (abortion):

1. Acute and sub-acute gonorrhea.
2. Acute and sub-acute vulvo-vaginitis and Bartholinitis of any origin, and also furuncles of the genital organs.
3. Erosions with secretion of pus from the cervix uteri.
4. Inflammatory processes of the ligaments and the peritoneum surrounding them.
5. All local purulent diseases and acute infectious diseases.[17]

It can easily be surmised that such legislation again sent abortions underground. According to a refugee physician, a gynecologist who before the war had worked in Leningrad, there was a constant stream of infections caused by unsterile abortions:

> . . . about 70 per cent of the women in our department were there because of complications following botched up abortions. Thus, the government's intention to increase the birth rate backfired [since] it had planned on an increase in births. Beds reserved for maternity cases had been increased, while those reserved for gynecology had been decreased; we had so many of these cases we didn't know what to do with them. And the mortality was very high . . .[18]

According to refugee testimony, doctors were under great pressure on the part of the population to perform abortions, and those who did it often fetched high prices for them.[19]

The law prohibiting the performance of abortions remained in force for nineteen years. During that period, further measures were taken to encourage motherhood and to increase family stability by increasing aid to mothers and by making divorces extremely difficult to obtain (1944).[20]

Occasionally, items appeared in the local press, indicating that such and such a person had been found guilty of performing criminal abortions and had been sentenced accordingly.[21] During all that time, the existence of the practice in Soviet Russia was officially described as due to a remnant of capitalistic consciousness among the less enlightened members of society. Outside Russia, it was maintained, abortions were widespread among all classes of the population: among the lower, "exploited" classes because of the terrible social and economic conditions and because of the stigma attached to illegitimate children; and

among the upper classes because of the desire to transmit capital intact from one generation to the other. Thus among "bourgeois" families, children were limited to one or two. Furthermore, in contrast to the Soviet Union, capitalist governments could not successfully struggle against abortions because they could not successfully improve the material conditions of the masses. Finally, private physicians "who constitute the greater part of the medical profession of bourgeois countries willingly perform illegal abortions and see in them one of the profitable items of their private practice."[1]

The first official indication that in the "land of Socialism" the survivals of capitalism still prompted women to have abortions, and physicians and other persons to perform such abortions, was a decree of the Praesidium of the Supreme Soviet dated August 4, 1954, entitled "On the Abolition of the Criminal Responsibility of Pregnant Women for Obtaining an Abortion," which nullified Paragraph 4, Article I, of the 1936 decree quoted above. No comments accompanied this law, nor was it discussed in the Soviet lay or medical press. Apparently, the reason for this decree was to make it easier for women who had had abortions and whose cases came to the attention of the organs of justice (hospitals and doctors were obligated to report cases of suspected abortion to the authorities) to give the name of the abortionist without incurring a penalty themselves. At the same time, this might make it easier for a woman to report to a hospital in case of complications, and might also tend to discourage abortionists from performing the operation, since they would be in greater danger of exposure. Apparently, this must not have had the desired effect because late in 1955 the Soviet government again reversed its stand on abortions.

1955 to Present

The Praesidium of the Supreme Soviet, in its session of November 23, 1955, passed a decree entitled "The Repeal of the Prohibition of Abortions." In the commentary preceding the text it noted that the measures enacted by the Soviet state to encourage motherhood and protect infancy, as well as the uninterrupted growth of the consciousness and culture of women who participate in all areas of economic, cultural and social life, permits "at the present time the lifting of the prohibition on abortions in the legal sense; the prevention of abortions may be secured through a further broadening of state measures to encourage motherhood and measures of an educational and explanatory nature." The decree then hints at the real reason for the change: "The repeal of the prohibition on abortions will permit the limitation of the harm caused to the health of women by abortions carried out outside of hospitals." Thus, the Praesidium of the Supreme Soviet, "in order to give women the possibility of deciding by themselves the question of motherhood . . . has decided to repeal the previous law on abortions."

The decree itself reads as follows:

1. Article I of the Decree of the Central Executive Committee and of the Council of Peoples' Commissars of the USSR, dated June 27, 1936 is abrogated.
2. Performing operations for the artificial termination of pregnancy is permitted only in hospitals and other medical institutions in accordance with an instruction of the Minister of Health of the USSR.
3. It remains a criminal offense both for doctors and for persons without special medical qualifications to perform abortions outside hospitals or other medical institutions.[22]

Thus, in the main lines, the decree is similar to the one promulgated in 1920. It again permits the performance of abortion and stipulates that it must be done only by qualified personnel in medical installations.* Again the decree is adopted not as a positive measure but as one largely aimed at reducing the harm caused to women by illegal operations. It brings the problem of abortions out in the open and permits the state to control it and minimize damages since legal measures were unable to eradicate the practice.

It is interesting, furthermore, that no publicity whatsoever had been given the measure as late as February, 1956. Outside the mention of the decree and its short preamble published in *Izvestiya* and *Pravda* there have been none of the commentaries, articles or editorials that usually accompany, elucidate and amplify newly adopted measures to the population.† A search in *Meditsinski Rabotnik* [*The Medical Worker*], the organ of the Health Ministry, fails to reveal even the text of the decree. One might therefore draw the following conclusions:

The present regime has recognized that—law or no law and regardless of socialist society — there will always be a substantial number of pregnant women who will seek abortions, for a variety of social, economic or personal reasons.

As long as this is so, and as long as women are desperate enough to submit themselves to abortionists and illegal operations, it is better to have them aborted in medical institutions, by physicians and under sterile conditions.

There is no point in publicizing the decree in the manner in which it was done in the twenties, for this

*According to evidence recently brought back from the Soviet Union, "the price for an abortion is 50 roubles, married or unmarried, no questions asked." At the artificial exchange rate this amounts to $12.50, in purchasing power it is closer to $5.00, an insignificant sum compared to what abortionists charged before the decree. (Personal communication from Morris H. Rubin.)

†Except for the following, which is drawn from the research plan of the Academy of Medical Sciences USSR, for 1956 through 1960: "XIII. Protecting the Health of Women, Mothers and Newborn Children, Specific Problem No. 7, CONTRACEPTIVES AND MEASURES TO INCREASE THE BIRTH RATE: The legalization of abortions has required the development of measures to protect the health and child-bearing capacities of women who have undertaken abortions. These same facts pose the problem of studying new and effective contraceptives which will protect women from the necessity of operations. In addition to this further study of the problem of childless marriages is required. *Responsible Executive*: Institute of Obstetrics and Gynecology, Academy of Medical Sciences USSR. *Executor*: Institute of Pharmacology, Experimental Chemotherapy, and Chemoprophylaxis, Academy of Medical Sciences USSR; Institute of Experimental Biology, Academy of Medical Sciences USSR." (Translated by Scott Adams, librarian, National Institutes of Health.)

might again encourage a "light-minded attitude toward family responsibilities" and might undermine family stability.

It may be surmised that physicians have received instructions asking them to discourage abortions, but permitting them to perform them if they are not successful.

That, depending on the consequences of the new law, and its effect on the birth rate, the regime may again, at any time, decide to prohibit abortions.

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MEDICAL PROGRESS

PATHOLOGY: DISEASES OF BONE*

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SOME fourteen years have elapsed since a Medical Progress report in this journal was last devoted to consideration of the pathology of diseases of bone,[1] although a cursory survey of a miscellaneous group of skeletal disorders from the radiologist's point of view[2] appeared in 1951. This apparent neglect seems to reflect pressures in many other directions during a period of unparalleled activity, rather than waning of interest in diseases of bone, neoplastic or otherwise, or lack of significant progress in understanding of them. Within the limited scope of this discussion, it will be possible only to highlight certain altered or new concepts with a view mainly to better orientation of medical men generally in a field that crosses many specialty boundary lines. If I refer frequently to my own publications, it is hoped that this will not be construed as a subtle expression of narcissism or as indicating any lack of appreciation of the work of others.

Primary Tumors of Bone

The sustained interest in bone tumors is evidenced by the publication in recent years of monographs by Geschickter and Copeland[3] (1949), Coley[4] (1949) and Lichtenstein[5] (1952). The last book incorporates in revised form many of the individually published papers of the preceding decade and attempts to convey a practical working knowledge of the benign and malignant tumors of bone, with emphasis on accurate diagnosis and therapeutic indications. Progress in the utilization of this essential information has been gratifying, on the whole, although there are still some radiologists who are apt to take "flyers" through unawareness of the probabilities involved and of the limitations inherent in their medium of interpretation. By the same token, there are still far too many pathologists who venture opinions having a bearing on treatment or prognosis, or both, on the basis of slides alone without fully realizing the importance of the pertinent roentgenograms and of an adequate history (including the surgeon's findings) for good clinical orientation. Also, some basic general principles calculated to be helpful in the recognition and appropriate treatment of bone lesions that may be neoplasms are summarized in a short paper[6] prepared for the American Cancer Society in 1954.

It seems worth while here to point out briefly some new or interesting facts about specific tumors of bone that have come to my attention since the publication of my book in 1952.

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Benign Chondroblastoma

Further experience with this distinctive benign tumor of bone (which is likely to originate in the epiphyses of large limb bones of adolescents, especially of the male sex) has firmly established the soundness of lifting it out of the morass of the "giant-cell-tumor variants" and classifying it among the neoplasms of cartilage-forming connective-tissue derivation. An occasional case is still reported as a giant-cell tumor,[7] and occasional cases are still overrated as sarcoma, especially chondrosarcoma, by pathologists who should know better. Apropos of age incidence, I have observed an unusual benign chondroblastoma originating in the capital humeral epiphysis of a thirty-seven-year-old man. This patient, however, was a pituitary dwarf with persistent epiphyseal cartilage plates, whose skeletal age was estimated at eighteen years.

Chondromyxoid Fibroma

Increasing awareness of this late-comer to the field[8,9] is evidenced by the publication of an appreciable number of case reports[10-15] within the past several years. Although most of these tumors were encountered in limb bones, especially of the lower extremity, a number have been described in ribs and in the innominate bone, and an unusual case was recently recorded by Benson and Bass[13] that involved the vertebral column at the level of the first to the third dorsal vertebra, encroached upon the spinal canal and caused symptoms of spinal-cord compression. The symptoms were effectively relieved by surgery and supplementary x-ray therapy. The tendency to overdiagnoses as sarcoma[9] is highlighted by a case in point reported by Ottolenghi and Petracchi[14] as chondromyxosarcoma in which an entire astragalus was removed, when curettement and packing with bone chips would have sufficed for cure. Incidentally, Dahlin[15] recently stressed the necessity for thorough curettement to avoid possible local recurrence.

In the same paper, Dahlin also expressed the view that chondromyxoid fibroma and benign chondroblastoma are closely related pathologically in that certain tumors held to be chondromyxoid fibromas may show fields reminiscent of benign chondroblastoma, and vice versa. It is true that one occasionally observes tumors composed of partially differentiated cartilage-forming connective tissue, some of which appear to be developing in the direction of chondromyxoid fibroma and others, in the direction of benign chondroblastoma. I have collected material from 8 such tumors, situated mainly in foot and hand bones. Although their cellularity and poorly differentiated character are calculated to arouse a strong suspicion of malignant change, their clinical behavior has not been at all aggressive. Study of this group of tumors is now in progress and strongly supports the concept that chondromyxoid fibroma and chondroblastoma are closely related members of the same family of tumors of cartilage-forming connective-tissue derivation — first cousins, if not siblings. It seems a mistake, however, and a step backward, not to maintain the separate identity of fully evolved tumors of the nature of chondromyxoid fibroma and benign chondroblastoma.

In this connection, I have also observed 2 unusual malignant mesenchymal tumors of bone showing chondroid differentiation in places. These appeared initially in the calvarium and vertebral column respectively, and subsequently in other skeletal sites, apparently reflecting multicentric origin. An appropriate niche for these comparatively rare, primitive chondrosarcomas will likewise have to be provided eventually in a complete classification of bone tumors.

Benign Osteoblastoma

An attempt has been made[16] to delineate more clearly the pathologic nature and appropriate treatment of certain benign tumors of bone of osteoblastic derivation, other than classic osteoid osteoma and osteoma, so-called. Their recognition is of practical importance in that they may be mistaken for giant-cell tumor, though without sound justification, or for osteogenic sarcoma and, as such, treated more aggressively than their benign nature requires. These benign osteoblastic tumors include the ones previously called osteogenic fibroma by me, as well as those referred to provisionally as "other osteoid tissue-forming tumors" in my classification of primary tumors of bone.[5] I have come to believe that there is no fundamental difference between these two subgroups and that for all practical purposes they comprise a single category of benign osteoid-forming and bone-forming tumors, which may be appropriately designated as benign osteoblastoma.

Most of the tumors recently reported by Dahlin and Johnson[17] under the heading of "Giant Osteoid Osteoma" are undoubtedly cases in point (benign osteoblastomas), although a few may be plausibly interpreted as genuine osteoid osteomas. I am reluctant to accept their proposed name, if only because the concept of classic osteoid osteoma[18,19] has become too firmly established and useful to be watered down by the inclusion of other tumors differing in a number of essential respects, clinically and radiologically, as well as pathologically. If the designation of giant osteoid osteoma is to have any usefulness within the present frame of reference, it might apply rather in a literal sense to the genuine osteoid osteomas of unusual size that one encounters occasionally. I have had the opportunity to observe 2 such remarkably large osteoid osteomas, 1 in the lamina of a lumbar vertebra of a child, and the other in the shaft of the humerus of a young adult, which measured as much as 5 cm. in its greatest dimension.

Osteogenic Sarcoma

The problem of devising means to reduce the appallingly high mortality in osteogenic sarcoma continues to be of grave concern. It appears that most

osteogenic sarcomas, even those recognized relatively early, have already seeded the lungs with tumor emboli by the time they are ablated, although several or many months may elapse before these emboli are sufficiently large and radiopaque to be discernible roentgenographically. Little, if anything, is gained by unnecessarily drastic surgery (for example, hip disarticulation for tumor in the lower femur), since recurrence in the amputation stump is exceptional. Nor does it seem logical to delay surgery pending intense irradiation of the tumor site; even if one could effectively destroy the tumor in this way, which is doubtful, the procedure is tantamount to locking the barn door after the horse has been stolen. With this in mind, I recently advocated irradiation of both lung fields to supplement amputation as an experimental therapeutic procedure, in the hope of destroying microscopic tumor foci before they become encased in a coat of armor, or at least reducing the spread to one or two metastatic sites that might be dealt with by segmental or lobar resection. That this is feasible is evidenced by the case reported by Goldenberg,[20] in which lobectomy for a solitary pulmonary metastasis from osteogenic sarcoma was followed by five-year survival. The stakes are sufficiently high to make it worth incurring the possible hazard of post-irradiation pulmonary fibrosis in the event of survival, as a calculated risk.

Periosteal (Parosteal or Juxtacortical) Osteogenic Sarcoma

Considerable interest has been evinced recently in this category of unusual neoplasms.[21-24] They develop apparently through progressive active proliferation of bone-forming periosteal connective tissue and appear on the surface of large limb bones rather than in their interior. The lower femur posteriorly is a site of predilection, though occasionally the tibia, the humerus or some other long bone may be affected. The lesions are said to be distinguished further from the conventional intramedullary osteogenic sarcomas by their relatively slow evolution, their more favorable course and their substantially higher survival rate.[21] The thesis advanced by Geschickter and Copeland[22] and by Dwinnell, Dahlin and Ghormley,[23] however, that *all* bulky lesions of parosteal ossification represent low-grade sarcomas from their inception and should be treated by prompt amputation even in the absence of unequivocal histologic evidence of malignant change, seems to be an unjustified, rather extreme point of view.[24] To be sure, the pathologist must be on the alert for this serious complication, and it is incumbent upon him to sample thoroughly all the tissue submitted and particularly to scrutinize the fields of connective tissue closely. The surgeon would be well advised in treating pertinent cases to require convincing proof of malignancy, rendered by an experienced observer, before resorting to radical surgery.

Nonosteogenic Fibroma of Bone

This benign tumor continues to turn up with surprising frequency, and many clinically silent lesions are discovered in the course of x-ray examination of the part after an injury or for some other reason. Its x-ray appearance is so consistently distinctive[5] that, in most cases, I now believe that biopsy or surgical removal is elective rather than mandatory. In the matter of tissue examination (in cases treated by curettement and packing with bone chips), pathologists generally are now less likely to mistake the lesion for giant-cell tumor or to be unduly alarmed, because of its compact spindle connective tissue, over the possibility of fibrosarcoma. As for the eventual fate of the tumor, I have not seen any case of spontaneous involution or disappearance in my own experience, although one wonders why it is not encountered more often in adults.

Giant-Cell Tumor

The more I see of giant-cell tumors of bone, the more wholesome my respect for them. Most of them in recent years have been aggressive or potentially aggressive tumors, graded as 2 or 2+, occasionally approaching 3 (on a 1:3 scale), although one must make allowance for the fact that the tumors that respond well to conservative treatment are not likely to be submitted for consultation. An appreciable number have manifested local recurrence after surgical extirpation, either in the surgical wound or in the operative field after resection. As notable cases among them, one may cite the appearance of a circumscribed tumor transplant in the surgical wound some months after curettement of a giant-cell tumor in the upper tibia, and in proximity to an extensor-tendon sheath after curettement of a tumor in the head of a metacarpal, as well as local recurrence in the soft parts after resection of the head of the fibula and in proximity to a bone graft inserted after resection of the lower end of the radius. In these circumstances, it is difficult and startling to realize that at one time there were some who maintained stoutly that giant-cell tumor did not represent a genuine neoplasm but a tissue reaction to trauma, hemorrhage or chronic irritation.

The validity of grading giant-cell tumors as indicated, as a guide to appropriate therapy and with a view to forecasting their probable clinical behavior, has been fully justified by my experience and has been supported by that of other observers[26] who have subjected their material to close scrutiny. To be sure, no method of grading tumors by cytologic criteria is infallible, and there may be occasional tumors of serious import that on initial examination may appear falsely reassuring. For the most part, however, the giant-cell tumors that pursue an aggressive clinical course are tumors of Grade 2 rather than Grade 1 initially, whereas those that eventually become frankly malignant (Grade 3) likewise reveal

a portent of this ominous tendency in previous tissue specimens. It seems worth noting once again that metastases from malignant giant-cell tumors may lose their original character. For example, in a case in point seen last year through the courtesy of Professor Dorothy Russell, of London, the widespread visceral metastases of a giant-cell tumor of the sacrum resembled rather undifferentiated fibrosarcoma and showed only a few dwarfed giant cells in some sites, and none at all in others.

In the matter of age incidence, I have observed several bona-fide giant-cell tumors in younger patients whose ages ranged between fifteen and twenty years. These constitute occasional exceptions to the useful rule that the odds are very much against anyone who ventures a diagnosis of giant-cell tumor in a patient below the age of twenty. Regarding less common sites of localization, I have now had occasion to observe a number of proved giant-cell tumors in the vertebral column, in metacarpal heads and even in a terminal finger phalanx (recurring locally after curettement). It is well to bear in mind, however, that rarefied, more or less expansile lesions of vertebras, particularly in children or adolescents, are likelier to represent aneurysmal bone cysts than genuine giant-cell tumors[27] and, as such, have a much better prognosis.

Ewing's Sarcoma

Further experience has convinced me more than ever that there are valid and useful pathological, as well as clinical, grounds for making a clear distinction between Ewing's tumor and primary reticulum-cell sarcoma (of bone marrow). So far as the patient is concerned, it means a difference between a survival rate of 5 per cent (or less) and one of 50 per cent. The fact that this distinction may not be easy when one is dealing with meager biopsy specimens showing extensive degeneration or necrosis does not negate the general principle. Regarding therapy I am now inclined to recommend irradiation rather than radical surgery. Irradiation may be expected to destroy the presenting tumor (if it has not already grown to bulky size) and to ameliorate the patient's complaints. It will not prevent the appearance of tumor foci elsewhere in the skeleton or eventual pulmonary metastasis, any more than surgery will. Since, with few exceptions, the anticipated survival period before dissemination of tumor is only a few years, five at the outset, there seems to be little point to subjecting the patient (and the family) to the trauma of loss of a limb.

Reticulum-Cell Sarcoma of Bone

In dealing with this tumor also, if the neoplasm has not already destroyed the bone or invaded the contiguous soft parts extensively, I am inclined to advocate x-ray therapy, employing a total tumor dose of about 2000 r. My experience, as well as that of others, has shown that this is capable of completely destroying the neoplasm and of effecting a cure, provided that tumor does not subsequently develop in other marrow sites, lymph nodes or elsewhere in the hematopoietic organs.

So-Called Adamantinoma of Limb Bones

Considerable interest continues to be evinced in this intriguing group of tumors, despite the fact that no more than about 27 cases have been reported to date.[28] Most observers in this country seem to favor the theory of origin from epidermoid or basal-cell inclusions (or both), irrespective of whether or not a factor of trauma is also invoked. Among pathologists in the British Commonwealth, Willis[29] has unequivocally endorsed this stand, whereas Hicks[30] and Lederer and Sinclair[31] have advanced the interesting suggestion that "adamantinoma" of the tibia is really synovial sarcoma in disguise.

Along more practical lines, clinical follow-up data are slowly accumulating to indicate that these tumors not only tend regularly to recur (locally) after attempts at surgical extirpation but may also extend to regional lymph nodes and even metastasize to the lungs. The importance of prompt ablation of the affected extremity once the diagnosis is clearly established is thus heavily underscored.

Chordoma

Reports continue to appear of relatively unusual chordomas developing at the lumbar, dorsal and cervical levels of the vertebral column, as well as of the more common ones in the sacrococcygeal region and the cephalad end of the axial skeleton. Among these, the paper by Congdon[32] furnishes a good deal of pathological detail of value, supported by clinical correlation.

For chordomas developing in the coccyx or the sacrococcygeal area, early recognition and consideration of radical bloc excision with a view to clearance are of paramount importance. That the situation is not altogether hopeless is evidenced by the outcome in a case in point observed by me in which the tumor was still well delimited, although it had already substantially destroyed the coccyx and was encroaching upon the sacrum. In this case meticulous bloc excision extending through the distal sacral segment apparently effected a cure; at all events, the patient is well over four years later, presents no indication whatsoever of local recurrence and has surprisingly little residual disability.

In the management of chordomas that are no longer amenable to successful treatment by surgery, cognizance should be taken of the claim of Friedman[33] that the result of high-voltage irradiation is substantially better than can be obtained by conventional technics.

Tumors of Periosteal Origin

A comprehensive discussion of tumors developing within periosteal connective tissue appeared last fall.[24] These comparatively uncommon neoplasms constitute a group unto themselves, and their pathological traits and clinical behavior must be determined empirically, rather than inferred by analogy. It is only in recent years that the field has been explored to any significant degree, and there is still much to be ascertained. Specific reference was made to periosteal fibroma, neurofibroma, lipoma and chondroma as the major benign tumors in point, and to fibrosarcoma, chondrosarcoma and osteogenic sarcoma as the malignant ones.

Also considered collaterally was the significance of cartilagenous or osseous metaplasia (or both) of periosteal connective tissue leading to the formation of juxtacortical tumorlike masses, and the incidence of eventual malignant change in such lesions. The position taken was one of opposition to indiscriminate radical surgery, advocated recently by Geschickter and Copeland[22] and by Dwinnell, Dahlin and Ghormley.[23]

Tumors of Synovial Joints, Bursas and Tendon Sheaths

A critical review of this group of tumors, considered as a single integrated unit, was published[34] last year. The conditions of osteochondromatosis and of pigmented villonodular synovitis, bursitis and tenosynovitis were also considered as tumorlike lesions of debatable pathological nature. Actually, relatively few undisputed tumors in these structures are observed with any appreciable frequency. The benign tumors that are encountered occasionally on the lining surfaces of articular capsules and tendon sheaths are mainly of the nature of lipomas and hemangiomas, derived from the supporting fatty connective tissue and its blood vessels.

The only primary malignant neoplasm of practical importance is synovial sarcoma. This ominous lesion is being recognized with increasing frequency now that its specific pathological features have been well defined, although the problem of effective treatment is still frustrating. In the past, delay in recognition, lack of a concerted plan of attack, temporizing and belated awareness of the seriousness of synovial sarcomas have all contributed to the picture of therapeutic failure. At present, a rational approach to the problem is still being striven for, and consideration should be given to measures, less drastic than initial amputation, that appear to be well conceived in the light of experience to date and, as such, deserving of further clinical trial; specifically (in tumors that are still relatively small and circumscribed), as wide clearance of the tumor as the situation will permit, prompt supplementary irradiation of the tumor bed and, in view of the significantly high incidence of lymphatic extension, close attention to the regional lymphatics and nodes. The recorded experience to date does not indicate convincingly that amputation of the affected limb is an attractive alternative to be used indiscriminately in all cases.

Histiocytosis X (Eosinophilic Granuloma of Bone, "Letterer–Siwe Disease" and "Schüller–Christian Disease")

The name histiocytosis X as a convenient broad general designation for the nosologic entity that includes eosinophilic granuloma, "Letterer–Siwe disease" and "Schüller–Christian disease," was proposed in a critical review[35] of the subject, covering especially the period from 1944 to 1953. In this article an attempt was made at a comprehensive reorientation on the basis of significant recent observations. These have lent additional strong support to the concept that the conditions mentioned represent closely interrelated manifestations of a single malady. There can no longer be any doubt that "Letterer–Siwe disease" and "Schüller–Christian disease" represent acute (or subacute) and chronic expressions, respectively, of the disseminated form of the malady. From the pertinent case records now available, one also gains the distinct impression that the lesion of eosinophilic granuloma represents the pathologic expression of an early, rapidly developing reaction to the etiologic agent. As such, it may appear not only within bone, where its presence was first recognized, but also in other sites, notably in lymph nodes, the skin, the oral cavity (gingiva, palate and so forth) and the anogenital region, as well as in the lungs and possibly other viscera (if the whole picture were to be revealed). The recognized types of clinical involvement can be grouped under the general heading of histiocytosis X and still be differentiated from one another so that useful distinctions having a bearing on treatment and prognosis are maintained.

As for the Christian triad, which has received so much attention in the past, it is now common knowledge that skeletal defects need not be situated in the calvarium and that many patients likewise fail to exhibit either exophthalmos or diabetes insipidus. For that matter, even when the full Christian triad is present, it does not necessarily establish a diagnosis of chronic disseminated histiocytosis X (Schüller–Christian disease) since it has also been observed in the acute form (Letterer–Siwe disease). As for diabetes insipidus in particular, it is now recognized that its manifestations may result directly from involvement of the pituitary body, its infundibulum or the tuber cinereum, in the absence of skull defects. In fact, skeletal defects in general should no longer be considered a *sine qua non* for diagnosis of the disease, since they may be absent, or if they do appear, they

may not become manifest until lesions in extraskeletal sites are already well established.

Finally, there no longer appears to be the slightest justification for listing "Schüller–Christian disease" among the primary disorders of lipid metabolism, along with Niemann–Pick disease and Gaucher's disease. Actually, the cholesterol analogue of the last two conditions is not "Schüller–Christian disease" but familial xanthomatosis (xanthoma tuberosum multiplex).

Aneurysmal Bone Cyst

Although this peculiar bone lesion was named[36] in 1942, it is only within the last several years that pathologists, radiologists and surgeons have become increasingly aware of it. Observations on sizable groups of cases and their clinical implications have now been published.[37-41] Interest in the condition has also been evinced abroad, in Holland, by Wieberdink[42] and, in England, by Taylor[43] and Barnes.[44] Its prevalence may be judged further by the fact that I have observed material from as many as 45 cases from 1948 to date, and the number seems to be growing steadily.

The condition is reported most often in children and adolescents, and it may appear in virtually any bone, although the long limb bones and the vertebral column are its commonest sites of localization. Here, the x-ray picture is sufficiently distinctive to enable anyone familiar with the condition to suspect it. The affected bone site, whatever its location may be, is completely transformed and ultimately resembles a peculiarly expanded, blood-filled sponge that, if untreated, may eventually reach impressive size. The communicating pools of venous blood within this reservoir are bordered by connective-tissue septa showing giant-cell reaction to hemorrhage and inordinate vascularity, as well as more or less conspicuous reparative new-bone formation by way of attempted reconstruction.

The progress of the condition may be arrested by thorough curettement and also by radiation therapy. The practical importance of its recognition, otherwise, lies in the fact that clinically it is often regarded as a neoplasm and hence may be treated more aggressively than is necessary. Specifically, the lesion is still sometimes mistaken for giant-cell tumor (atypical, subperiosteal giant-cell tumor, so-called), for hemangioma and even for osteogenic sarcoma, although without any real justification. Significant information regarding therapeutic indications is now available, and, in particular, one is becoming increasingly aware of the hazards of injudicious treatment, of prolonged neglect of the condition and of attempts to treat lesions of the vertebral column by surgery primarily.

Hereditary Ochronosis

For those who have not already seen it, brief mention is made here of a recent paper[45] describing the gamut of pathologic changes observed in fully developed ochronosis and attempting to bring the condition into sharper focus in the light of recent pertinent advances in genetics and biochemistry. Far from being a harmless curiosity, as is often implied, hereditary ochronosis results eventually in more or less disabling arthritis and ankylosing spondylitis of a specific nature. The development of calcific aortic stenosis is another serious sequel, observed in 2 autopsied cases. Still other deleterious effects are severe arteriosclerosis, ochronotic nephrosis, pigment deposition in the pancreatic islets and the formation of pigment calculi in the urinary tract.

Pathologic Changes in Gout

Renewed interest has been manifested in gout in recent years, and although much still remains to be clarified, the advances of the past decade are undoubtedly impressive. Appreciable insight has been gained into the basic nature of this intriguing disorder of purine metabolism, and this has had its practical application in more effective treatment. In keeping with these clinical and biochemical advances, an attempt has been made by Lichtenstein, Scott and Levin[46] to keep the fund of pertinent pathological observations up to date. This paper, which will be available shortly, surveys the findings in 11 autopsied cases and discusses the gamut of pathologic changes observed in fully developed, chronic tophaceous gout, particularly the skeletal, cardiovascular and renal alterations. A detailed account is rendered of the findings in 1 of these cases, an instance of chronic deforming gouty arthritis of unusual severity, characterized further by remarkable calcification and ossification of tophaceous deposits.

Skeletal Developmental Anomalies

Even cursory consideration of the accrued clinical and pathological data pertaining to the manifold systematized anomalies of skeletal development would require a lengthy article in itself. Suffice it to point out here, for those who are not already familiar with it, that the atlas presented by Sir Thomas Fairbank[47] in 1951 provides convenient basic orientation, as well as many valuable observations on specific disorders.

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MEDICAL INTELLIGENCE

IODIDE "MUMPS" AFTER INTRAVENOUS UROGRAPHY*

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SALIVARY-gland swelling is an infrequent manifestation of "iodism" or iodide idiosyncrasy, occurring after therapy with inorganic iodine compounds. Its appearance may suggest the possibility of mumps or stone in the salivary ducts and lead to embarrassing, tedious and sometimes costly investigations. The following cases are reported because salivary-gland swelling occurred as a sequel to intravenous urography with new organic iodide preparations, diatrizoate sodium (Hypaque) and sodium methylglucamine diacetylamino-triiodobenzoates (Renografin), and introduced the diagnostic possibilities of epidemic parotitis and salivary-duct calculus.

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CASE REPORTS

CASE 1. M.E., a 68-year-old merchant, complained of right-sided facial swelling and tenderness. He had recently had a complete medical survey, and no organic disease was uncovered. Physical examination revealed an afebrile, normal man with obvious swelling of the right and enlargement of the left parotid gland on palpation. Upon further questioning, it was learned that he had undergone intravenous urography 2 days before he became aware of the facial prominence. After a preliminary test dose, his urologist had injected 30 ml. of Hypaque intravenously, after which there had been no reactions. Renal function had proved to be completely normal by this examination, as evidenced by prompt visualization of the kidneys, pelves and ureters of both kidneys. X-ray study gave no evidence of stone in the salivary-gland regions. The swelling had completely abated at the end of 6 days.

CASE 2. B.H.T. MacK., a 62-year-old engineer, entered Beth Israel Hospital for the 1st time because of weight loss, nausea and vomiting. Nothing in his past or present history suggested a cause for salivary-gland disease. His history disclosed an old shrapnel wound involving the left side of the chest and pulmonary tuberculosis followed by left-sided fibrothorax 30 years previously. As a part of a clinical survey, cholecystography was performed on January 17, 1956. 6 days later, an intravenous pyelogram was performed with 20 ml. of Renografin. Two days later both submaxillary glands grew to the size of small plums. On the following day, they had begun to diminish in size and, 6 days later, had returned to normal size. Because of the recent intake of organic iodide, the age of the patient, the absence of fever

and the history of exposure, epidemic parotitis was discarded as the diagnosis.

Discussion

These cases of "iodide" mumps relate salivary-gland swelling to recent administration of organic iodides.

Organic iodides are valuable agents for contrast visualization, and are widely employed in radiology. Fortunately, immediate, dangerous side effects are infrequent, and these substances may be given if recommended precautions are followed before and during their administration. Although the risk of immediate reactions, characterized by urticaria and laryngeal edema, is well recognized, iodism and delayed serum sickness, consisting of fever, arthralgia, lymph-node enlargement and eosinophilia, have not been reported.[1] Chronic iodide poisoning, or so-called iodism, is usually a sequel to iodine therapy with inorganic compounds and will occur in all persons if the dose is high enough. The symptoms were well known during the preantibiotic era, when these substances were often employed in the treatment of syphilis. Respiratory manifestations are usually initiated with increased salivation, brassy and burning taste in the mouth and soreness of the teeth and gums. Coryza and its attendant unpleasantness are prominent. Fluid accumulation in the pulmonary tree may lead to pulmonary edema, particularly in susceptible cardiac patients with early failure of the left ventricle. Inflammatory reactions involving the salivary glands, pharynx, larynx and tonsils may appear. Skin lesions, sometimes fatal, have been reported as iododerma. Gastrointestinal disturbances, such as anorexia, nausea, vomiting and diarrhea have been described. Cachexia, fever and depression have all been included in the clinical state known as "iodism."

Since iodide is present in all exocrine secretions that ordinarily contain chloride, it is not surprising that the symptoms of iodism are related to the secretory processes concerned with gastric-juice,[2] saliva and sweat production. At low rates of secretion, the concentration of iodide in saliva may be thirty times that in plasma.[3] Except for its thyroid localization, the distribution of iodide follows that of the other halides, chloride and bromide, being largely confined to the extracellular-fluid compartment. It can enter the red blood cell and may exchange with a small amount of chloride in the fixed tissue cells. It differs from chloride in its spinal-fluid distribution since large increases of the plasma iodide level are not appreciably reflected in the spinal fluid.[4]

The chief excretory route of iodide is renal, and the kidneys vie with the thyroid gland for this halide. Its plasma clearance is 30 ml. per minute, or 25 per cent that of inulin clearance in man. Unlike bromide, which cumulates because of preferential renal excretion of chloride, iodide is excreted independently of chloride, its renal clearance being constant over a very wide range of plasma concentrations.[5] Patients on diets low in sodium chloride will therefore have no impairment of iodide excretion provided renal function is intact. As is often true with other drugs,[6,7] annoying cumulation of iodides will occur much sooner when there is marked renal impairment, and symptoms of iodism will appear more frequently if these substances are used in the course of renal insufficiency. This may be more important in patients who are not undergoing renal investigation and who would therefore be less likely to be studied from the point of view of renal decompensation. When multiple contrast visualization is contemplated, it seems a wise precaution to employ intravenous technics first, to avoid subsequent dangerous anaphylactoid reactions, which are more likely to follow parenteral or intravenous therapy.

Summary and Conclusions

Two cases of salivary swelling that followed the intravenous administration of organic iodides are presented. Both appeared two days after exposure and disappeared within a week. The history of recent exposure to organic iodides during contrast visualization should be a consideration in the differential diagnosis of parotid or submaxillary adenitis in adults.

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ABSENCE OF BETA-GLOBULIN FRACTION IN THE SERUM PROTEIN OF A PATIENT WITH UNEXPLAINED ANEMIA*

Report of a Case

Cecilia Riegel, Ph.D.,† and Dorothy Thomas, B.S.‡

PHILADELPHIA

IN the following case the beta-globulin fraction was almost completely absent from the serum protein.

Case Report

An 85-year-old woman was admitted to the hospital for the 1st time on May 8, 1953, with the chief complaints of

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weakness, dizziness, dyspnea and some edema of the ankles. At this time the hemoglobin was 3.1 gm. per 100 ml., and the red-cell count 1,040,000. She was in cardiac failure. A number of blood transfusions relieved symptoms and increased the hemoglobin to 9.5 gm. per 100 ml. She was discharged with no diagnosis of the cause of the anemia. Subsequently, she returned to the hospital every few months for the next 3 years. During this period, in spite of numerous transfusions, the hemoglobin concentration never rose above 7 gm. per 100 ml. Bone-marrow studies showed erythrogenic hyperplasia, and a gastric test meal showed free hydrochloric acid. Stools were reported as containing occult blood on some occasions, and none on others. Repeated x-ray study of the gastrointestinal tract revealed nothing abnormal except 3 duodenal diverticula. Cystoscopic examination showed chronic cystitis; *Escherichia coli* was cultured from the urine. During this period the patient received over 40 blood transfusions and much medication, including ferrous sulfate, crude liver extract, Lextron, Lirumin, Rubramine, vitamin B_{12} and folic acid. The administration of iron probably accounts for at least some of the positive occult-blood tests in the feces. Clinical improvement was manifested only after blood transfusion. Diagnosis of the origin of the anemia could not be made.

Two months before death a blood urea nitrogen of 50 mg. per 100 ml. was noted, and 1 month later the patient was hospitalized because of a stone in the right ureter and renal enlargement. She died on January 25, 1956. Post-mortem examination disclosed a normal left kidney, pyonephrosis of the right kidney, with renal abscesses, and a calculus in the right ureter. The spleen, abdominal lymph nodes and liver showed advanced hemosiderosis, with early lobular fibrosis of the liver. The vertebral marrow was cellular, with active normoblastic and granulocytic proliferation. The cause of the anemia was not ascertained.

Filter-paper electrophoresis on serum obtained 2 days before death revealed an extremely low or absent beta-globulin fraction, and electrophoresis of blood obtained at post-mortem study confirmed this finding (Fig. 1).

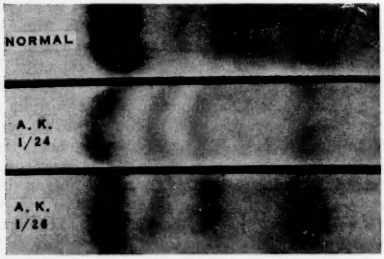

FIGURE 1. *Electrophoretic Patterns in a Patient with Anemia of Unexplained Cause.*

DISCUSSION

The beta-globulin fraction of the serum proteins contains the iron-binding globulin (transferrin, siderophyllin) by which iron is transported to the tissues. The almost complete (or complete) absence of this protein fraction would mean that the normal pathway of transportation of iron was not available. Also, it might thus be impossible to effect a transfer of iron from ferritin to the circulating iron-binding protein. Analyses of the serum revealed an iron content of 75 microgm. per 100 ml. (normal average, 110 microgm.). The unsaturated iron-binding capacity was 0, indicating that if this patient had any iron-binding protein it was completely saturated and that she had no reserve protein for use in increasing the amount transported. Since electrophoresis showed practically no protein available for combination with iron, it is interesting to speculate whether the iron found in the serum was present as inorganic iron. The method of analysis makes no differentiation, and dialysis was not done. This lack of reserve protein explains why the administration of ferrous sulfate produced no improvement.

In addition to the anemia this patient had had a chronic cystitis for some time, and on her next to last admission was found to have a stone in her right kidney, with pyonephrosis. The stone may have existed for some time, but she did not complain of pain from this source on earlier admissions. A low iron-binding capacity, as evidenced by determination of serum iron and iron-binding capacity, has been reported in cases of chronic infection. However, in such patients some unsaturated iron-binding protein has always been present, as evidenced by an increase in serum iron on addition of ferrous sulfate.

The patient was found at autopsy to have extensive hemosiderosis deposits in many tissues, including the liver, spleen, pancreas and, especially, the lymph nodes. Such large tissue deposition seems to argue for the presence of transferrin to transport iron to these tissues, but she had at least 40 blood transfusions during a three-year period, and iron deposits could have resulted from the transferrin (and hemoglobin) present in the transfusion blood. The presence of such extensive hemosiderosis might also be advanced as a reason for considering the lack of beta globulin to be due to a blocking (and consequent nonfunctioning) of the reticuloendothelial system — that is, that the lack of beta globulin is the result of a nonsynthesis at a late stage of the disease (if the reticuloendothelial system is concerned in the synthesis of this protein) and not per se the cause of the anemia. However, it seems unlikely, if the reticuloendothelial system is involved in protein synthesis, that one protein fraction would be affected to the exclusion of others. It is unfortunate that electrophoresis on blood at earlier stages of the disease was not done.

It seems possible that this patient's anemia resulted from a lack of beta globulin. No previous report of such a condition has been found in the literature.

BY THE LONDON POST

Divine Healing — Home Care

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THE British Medical Association recently published a report on divine healing that was prepared in response to a request from the Commission set up by the archbishops of Canterbury and York. The Commission was anxious to know whether the medical pro-

fession could produce evidence of spontaneous recoveries from apparently incurable diseases, or of accelerated recovery from serious illness, that followed such spiritual ministrations as the laying on of hands, unctions or healing services. They also asked for the medical profession's views on whether such practices ever caused patients to delay seeking medical advice.

The committee of the Association that prepared the evidence sent out a questionnaire to a number of doctors, and this was completed by 70 physicians. Unfortunately, the material submitted in the replies was meager and uncritical. The committee found no definite evidence of spontaneous recovery among the replies. It pointed out that there are difficulties in assessing a cure. The patient's criterion of cure is freedom from symptoms whereas the doctor requires that there shall be a restoration of normal functions. Furthermore, the natural history of many diseases is characterized by spontaneous relapses and remissions, but the symptoms in psychosomatic disorders are notoriously variable in severity. The committee believes that most cures claimed for spiritual healing are explained by mistaken diagnosis or prognosis, or by spontaneous remissions. It was informed of a few patients who apparently suffered as a result of delay in consulting a doctor, and, as might have been expected, several of these related to Christian Science teaching and practice.

In spite of these largely negative findings in its investigations, the committee had no doubt about the value of religion in assisting the patient in his illness. Although unable to make any definite statement about the value of such ministrations as healing services and the laying on of hands, the members believed that the patient may be helped by an attitude of mind free from fear and morbid apprehension and were convinced of the value of public or private prayer in this respect.

Indeed, the committee stressed the great importance of religion in keeping up the patient's morale in a serious illness. Although such a method of keeping up morale may be chiefly the concern of the clergyman, the physician, by his quiet confidence, may do much to give the patient reassurance and peace of mind.

This view, of course, is not easily accepted by members of the clergy who hold strong views on what may be called faith healing, and it is with such persons that co-operation between the physician and priest becomes difficult. This has been stressed in the correspondence stimulated by the publication of the British Medical Association report. One correspondent points out that in their approach to disease the physician and the priest may be almost diametrically opposed because the Church insists on blind faith whereas the doctor is taught to accept only knowledge founded on observation and experiment. Such differing points of view are confusing for the patient, and if intelligent, he is likely to want to reject either one or the other.

It seems clear that there are considerable dangers in any suggestion of dual care of the patient. In his best interests he must remain under the single care of his physician, and co-operation with the clergyman is likely to be most beneficial when this is restricted to the practice of the orthodox ministrations of the Church, which can play an important complementary part in the management of many cases. The only exception to this principle is probably in cases of functional disorders in which the physician believes that the priest is likely to be of much greater help to the patient than any physical medicine. Most doctors would probably agree that collaboration between the clergy and the physician is desirable and should be beneficial to the patient. It could, however, have the reverse effect if the difficulties were not appreciated and if either profession sought the credit for the cure. The object is to restore the patient to health, and all means must be used. In physical illness the physicians and surgeons may perhaps humbly be regarded as the instruments of the Divine, and the ministers of the Church must support them in their work and give their patients all the spiritual encouragement possible. It must surely never be a question of "prayers before penicillin."

* * *

One of the main anxieties both to those working in the National Health Service and to those administering it is the rising demand upon the hospitals. The number of patients admitted to hospitals within the Service has risen year by year since 1949. Many of the hospitals inherited by the Ministry of Health are obsolete, and strong views have been expressed by many senior consultants on the urgent need for extensive rebuilding and for implementing the program of new building approved by the Government last year. Unfortunately, the cost of such work continues to rise, and the hospital service is by far the most expensive part of the National Health Service. Because of this, and because there are many who believe that the right place to be sick is at home, there is a current emphasis on the advantages of home care. In an introduction to a symposium on home care and nursing in the *Practitioner,* Dr. G. E. Godber has pointed out that the Service depends primarily upon comprehensive home care, with hospitals and specialist services only for diagnosis and treatment of illness outside the scope of the family doctor and his supporting team. The extent of this supporting team is probably not fully appreciated. The modern general practitioner has available a whole series of facilities provided through the local medical officer of health. These include home nurses, midwives and mental-health workers. In addition he is able to recommend that domestic help be provided in cases of need through the Local Authority Home Help Service.

The general practitioner can also avail himself of the services of the health visitors, whose work has probably been as instrumental as any other influence in reducing infant mortality. As the *Times* has

pointed out, the health visitor was launched against the Edwardian complex of poverty and parental ignorance of the elements of healthy living that was handicapping children because the ordinary doctor was virtually unable to cope with it. Today, she visits most households with young children each year and sees the older children at school. The scope of her work has recently changed as general living conditions have improved, and since she is at present always a trained nurse, she is available for assisting households whose difficulties derive from such conditions as tuberculosis, diabetes, chronic illness or old age.

Quite apart from the assistance offered to the general practitioner by the services of such people as these, he is able, through the domiciliary service of the National Health Service, to call upon hospital consultants to visit patients in their homes. Thus, at no cost to the patient a general practitioner may obtain consultant advice at the patient's own bedside and continue to care for the patient in his home. With all these facilities at his disposal it should be possible to lighten the load on the hospital service, and the proper use of the services provided should help to restore the family doctor to his rightful position of being the backbone of the profession. Many general practitioners are doubtless fully aware of the opportunities available. On the other hand there are many who are overworked and frankly glad to be relieved of the care of seriously ill patients. The same thing may be said of many relatives of patients requiring constant nursing care, but not strictly needing hospitalization.

It is clearly important to regard the whole range of medical care available under the Service as a unit, the facilities in hospital and in the home being complementary to each other. The vast national expense involved puts a great responsibility upon those working in the Service and those sharing its benefits to use any of the facilities with discretion. At present there is no doubt that the right trend is toward shifting the emphasis from hospital care to home care.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 42351

PRESENTATION OF CASE

A sixty-three-year-old schoolteacher was admitted to the hospital because of dyspnea.

Four months previously he was admitted to another hospital for three months because of an acute myocardial infarction. While he was hospitalized, there were episodes of pain in the chest that responded poorly to nitroglycerin and rest, and were occasionally associated with a cough productive of blood-tinged sputum. He was discharged, improved, on Dicumarol. About four hours before entry he became acutely dyspneic and coughed up blood-tinged sputum. Pulmonary rales and hypotension were noted by his physician.

Physical examination revealed a well nourished, dyspneic, cyanotic man. The veins of the neck were not distended. Examination of the chest showed coarse, bubbling rales throughout both lung fields. The heart was slightly enlarged to the left. There was atrial fibrillation at a rate of 140. No murmurs were audible. Examination of the abdomen was negative. There was no peripheral edema.

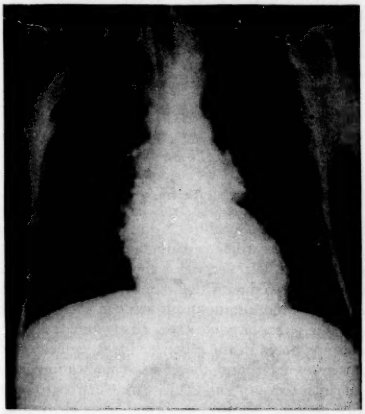

FIGURE 1. *Roentgenogram of the Chest Taken on Admission, Showing Moderate Enlargement of the Ventricle and Prominent Vascular Markings, Particularly Conspicuous in the Right-Upper-Lung Field.*

The temperature was 100.4°F., the pulse 120 and irregular, and the respirations 30. The blood pressure was 95 systolic, 55 diastolic.

The urine gave a + test for albumin. Examina-

tion of the blood revealed a hemoglobin of 12.6 gm. per 100 ml. and a white-cell count of 19,600, with 86 per cent neutrophils. The prothrombin content was 18 per cent. Culture of the sputum grew out abundant alpha-hemolytic streptococci and a few *Haemophilus influenzae*; three specimens were negative for acid-fast bacilli. X-ray films of the chest demonstrated cardiac enlargement, chiefly in the region of the left ventricle; the upper lobe of the right lung showed a diffuse, patchy, linear infiltration, with several more radiolucent areas in the apical segment; the pulmonary vessels were engorged; a calcific lesion was noted in the posterior basal segment of the right lower lobe, and there was calcification in the right hilar region (Fig. 1). An electrocardiogram (after digitalis) showed a normal sinus rhythm at a rate of 70; the PR and QRS intervals measured 0.12 and 0.10 seconds, respectively; the ST segments were slightly elevated in Lead 1, markedly depressed in Leads 2, 3 and aVF, significantly elevated in Lead aVL and depressed in Leads V_4 and V_5; the T waves were inverted in Lead 1 and diphasic in Leads V_4 and V_5; the Q waves were very small in Lead aVL (Fig. 2).

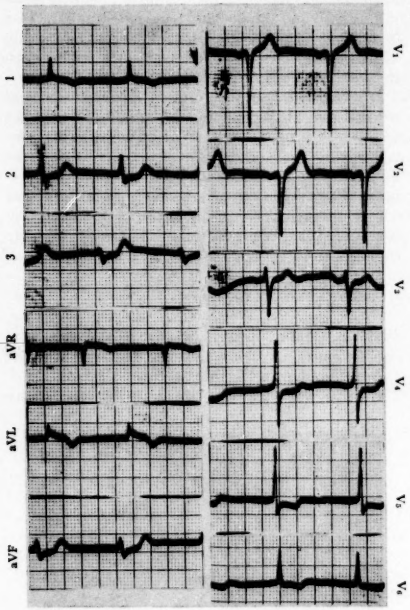

FIGURE 2. *Electrocardiogram.*

With digitalis, Mercuhydrin, oxygen and penicillin therapy the chest became clear except for basal rales; the blood pressure rose to normal, and the pulse became regular and fell to normal. The patient continued to cough up blood-tinged sputum. On the day of admission there was an episode of mild oppression in the chest anteriorly. Dicumarol was continued during the first three hospital days and then omitted. The prothrombin content during this time rose from 12 per cent to 42 per cent. On the third hospital day there was another episode of oppression in the chest that was relieved with oxygen. On the fifth hospital day atrial fibrillation was again noted. X-ray films of the chest demonstrated an increase in the diffuse, patchy, linear infiltration in the right upper lobe; a similar infiltration was now seen in both lung fields, and there was an area of density with consolidation involving the left lower lobe; fluid was noted posteriorly in the right pleural space (Fig. 3). With Cedilanid, given intravenously, and quinidine the cardiac rhythm reverted to normal. On the next day there was an acute episode of precordial pain that was associated with pallor, perspiration and dyspnea. An electrocardiogram showed no significant change. During the evening he was noted to be perspiring, cyanotic and cold, with an unobtainable blood pressure, a weak thready pulse, gasping respirations and bubbling rales throughout the chest.

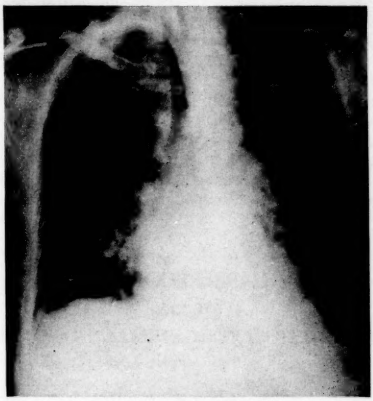

FIGURE 3. *Roentgenogram of the Chest Taken on the Fifth Hospital Day.*

He died five hours later, on the seventh hospital day.

DIFFERENTIAL DIAGNOSIS

DR. BRYAN WILLIAMS, JR.*: I should like to see what I can do with this protocol without the usual help from the x-ray films or Professor Einthoven's somewhat fickle galvanometer string. This man's illness began with a myocardial infarct about four months before admission. The course was protracted for an uncomplicated myocardial infarct, and the his-

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tory of blood-tinged sputum, chest pain and dyspnea suggests that he had pulmonary infarcts at that time. The acute episode for which he was admitted to the hospital was characterized by dyspnea and hemoptysis. He was noted to have transient attacks of atrial fibrillation. The white-cell count was somewhat elevated and the hemoglobin was slightly low, but the prothrombin time was within the range that most of us accept as being therapeutic and yet relatively safe. This acute episode responded to a little necessary "polypharmacy," but in the next week he had another transient episode of atrial fibrillation; in addition, he had pain in the chest, dyspnea and pulmonary edema. The last day was very stormy, with pulmonary edema and shock.

A note is made in the protocol that culture of the sputum yielded some organisms that may have been part of the normal flora. Occasionally, pneumonitis in an adult may be caused by Pfeiffer's bacillus, but most adults seem to be as resistant to this organism as children are susceptible to it. Pneumonia caused by *H. influenzae* is characterized by hemoptysis throughout its course and not merely in the acute phase. This is presumably due to the proclivity of this organism to ulcerate rather than to suppurate. This is mentioned as an aside. I do not think that the patient under discussion had a respiratory-tract infection.

Could this patient have died of a complication of the Dicumarol therapy? We are always alert to this possibility in any patient on anticoagulants. There was no evidence that he had massive exsanguination. There was no progressive distention of the neck veins or pulsus paradoxus to suggest a slow accumulation of blood in the pericardial sac, either from a hemorrhagic pericarditis secondary to a myocardial infarct or from a slowly rupturing heart. Although it is entirely possible that the last episode was caused by a cardiac rupture, I should not think that it was the primary difficulty.

Despite the fact that the patient first had a myocardial infarct, I think that the last week was probably characterized by repeated pulmonary infarcts, which contributed significantly to his death. This idea is supported by the transient atrial fibrillation, which frequently occurs in repeated pulmonary emboli. The other symptoms are relatively nonspecific in themselves.

By this initial speculation two other avenues of speculation are opened: one is the origin of the emboli to the lungs, and the other, the question whether there was an associated recent myocardial infarct. Despite the fact that emboli from mural thrombi occur in patients with myocardial infarcts, there is still about a 3:1 chance that emboli to the lungs come from the veins of the legs. Infarction of the right atrium is unusual, as is that of the right ventricle, presumably because there is some nutrient to these thin-walled chambers from the cavitary blood. Most of the mural thrombi from the right side of the heart are from septal infarcts. In the absence of peripheral venous disease, the best I can do is play the odds on whether these emboli came from the veins of the legs, which furnish most of the emboli even in patients with myocardial infarctions, or from the right side of the heart. I think they may have originated in the leg veins.

It is interesting to speculate about whether the patient had a recent myocardial infarct, perhaps precipitated by the pulmonary emboli. We are all aware of the relation between acute myocardial infarcts and pulmonary infarcts in patients with preexisting impaired coronary circulation.

In summary, I think that the patient had an old myocardial infarct, a recent myocardial infarct and multiple pulmonary infarcts during both the previous and the final illnesses. The leg veins were the most likely source of the pulmonary emboli, although they may have arisen from a mural thrombus. He may have had a rupture of the heart. I should like to stick to these diagnoses, regardless of what shows up when the lights in the x-ray box come on; I should like to abandon any privilege I may have of changing my mind after I see the films.

DR. FREDERICK M. TOMCHIK: In the x-ray examination of the chest made on admission the heart appears moderately enlarged; the left ventricle is the chamber predominantly involved. The pulmonary vessels are congested. In the right-upper-lung field the bronchovascular markings are definitely more prominent than elsewhere, although the appearance there is still apparently due only to pulmonary vascular congestion, as far as I can tell (Fig. 1). I do not believe I can say that there is any definite pulmonary infiltration there. The radiolucency of the right-lower-lung field is interesting. On the lateral view there is a suggestion of some posterior displacement of the lower portion of the right major fissure and possibly a slight upward bulge of the right minor fissure. It is conceivable that there is some obstructive emphysema involving the right middle lobe, but the findings are not clear-cut. The localized emphysema is not obvious on another posteroanterior film made the same day. There is blurring of the left leaf of the diaphragm and a pleural effusion on the left. The patient has a low flat diaphragm and increase in the anteroposterior diameter of the chest. Four days later there is a marked increase in the degree of pulmonary vascular congestion; all portions of the lung now appear to be involved (Fig. 3). There is a pleural effusion of moderate size at both bases. The density mentioned in the protocol, I believe, is in the right-lower-lung field rather than the left. I do not identify that in the lateral view. It could be a localized pneumonitis or edema. I suppose that it could be a pulmonary infarct, but the appearance is not specific.

DR. BENJAMIN CASTLEMAN: I gather, Dr. Williams, that these findings are in line with the diagnosis you have made; they would not sway you.

DR. WILLIAMS: I should rather not say!

DR. CASTLEMAN: Dr. Currens, what do you think this man had?

DR. JAMES H. CURRENS: The arrhythmia — that is, the atrial fibrillation — that developed is unusual in the garden variety of myocardial infarction except possibly with involvement of the lateral wall of the left ventricle, which is suggested by the electrocardiogram. I do not know whether it is due to the technic, but in the second film there seems to be more prominence of the hilar vascular markings, suggesting thrombosis of the pulmonary arteries on the basis of recurrent emboli.

DR. TOMCHIK: They were both taken at the same time. The second film was probably taken because of inadequate exposure on the first. I think the difference is a matter of technic.

DR. CASTLEMAN: Dr. Friedlich, you saw this patient. Will you comment?

DR. ALLAN L. FRIEDLICH: There were two points that bothered us. One was the atypical feature of the initial episode of pain, which was pleuritic from the onset and was diagnosed as myocardial infarction in the outside hospital. The electrocardiograms, I assume, we are not allowed to talk about.

DR. WILLIAMS: Let's discuss them now.

DR. CASTLEMAN: The first electrocardiogram was read by Dr. Williams himself; he interpreted it as "an abnormal electrocardiogram, suggesting a recent, high lateral myocardial infarct as evidenced by the ST-segment elevation, T-wave inversion in Lead aVL and reciprocal changes in Leads 2, 3 and aVF; a second tracing with precordial leads one interspace higher than usual may aid in determining the changes seen in Lead aVL in the present tracing." In the second tracing two days later he saw no significant change.

DR. WILLIAMS: Lead aVL "looks at" the lateral surface of the heart; therefore, changes that are not found with the usual precordial leads may be picked up in that lead. If the precordial leads are placed one interspace higher than usual, a high lateral infarct may be detected.

DR. CASTLEMAN: I gather from this report that you interpreted this as a recent myocardial infarct. You said nothing about an old infarct.

DR. WILLIAMS: In the presence of ST-segment elevation I think one is obliged to call it recent until the previous history is known. Persistent ST-segment elevation may be noted in an aneurysm of the heart developing after a myocardial infarct.

DR. FRIEDLICH: The second point that was unusual about this case was that when the patient was not dyspneic the x-ray film showed tremendous changes suggesting an infiltrative lesion in the right lower lobe, advancing very rapidly. For that reason we leaned toward an infiltrative process and away from infarction or congestion.

DR. LEONARD W. CRONKHITE, JR.: The only retrospective comment that I have is that I wish we had had Dr. Williams's restraint. Having ordered those x-ray films, however, we felt obliged to look at them. On the first set we were so convinced that the process was in the upper lobe rather than the lower lobe that I asked Dr. Kenneth T. Bird to see the patient. He agreed that he could not explain the changes on a cardiac basis and thought tuberculosis was the most likely diagnosis. As the course became worse and worse, we actually started to treat the patient concurrently with antituberculosis drugs. When the second set of films showed that the lower lobes were involved, we were less certain about the diagnosis of tuberculosis.

DR. CASTLEMAN: Dr. Pittman, have you a comment?

DR. HELEN S. PITTMAN: I think this is congestion of the lungs.

DR. CASTLEMAN: Not infarction?

DR. PITTMAN: The only thing at all suggestive of an infarct that I can see from here is the shadow along the left side of the heart above the diaphragm in the first film. My money is on congestion and not infarction. My mind, too, was made up before I saw the films; I did not change it after I saw them.

DR. WILLIAMS: In 1940 Hampton and Castleman* described linear infiltration as evidence of old pulmonary infarcts. Is this the same thing that we are seeing now?

DR. CASTLEMAN: The infiltrations were not quite like this; they were much more definite. Do you agree, Dr. Tomchik?

DR. TOMCHIK: Yes; these look like pulmonary vascular congestion, not like a scar of an infarct.

DR. CASTLEMAN: I notice that the serum transaminase was not determined.

DR. CRONKHITE: That was my own personal rebellion.

CLINICAL DIAGNOSES

Multiple pulmonary emboli.
Coronary-artery disease.
Myocardial infarction.
Tuberculosis.

DR. BRYAN WILLIAMS, JR.'S, DIAGNOSES

Myocardial infarcts, old and recent.
Multiple pulmonary infarcts, with emboli originating in leg veins.

ANATOMICAL DIAGNOSES

Myocardial infarction, recent and old.
Pulmonary congestion, severe.
Coronary sclerosis, severe.
Hydrothorax, bilateral.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: This patient, in addition to an

*Hampton, A. O., and Castleman, B. Correlation of post mortem teleoroentgenogram with special reference to pulmonary embolism and infarction. *Am. J. Roentgenol.* 43:305-325, 1940.

old myocardial infarct involving the interventricular septum, which occurred four months before admission, had a recent infarct of the anterior lateral aspect of the left ventricle, which I think occurred on the day of admission. It was about seven days old and contained neutrophils that were degenerating; there were no mural thrombi. There was, of course, severe coronary-artery disease. The lungs showed only congestion. There was pleural fluid on both sides. We examined the lungs extremely carefully for infarcts — we went down every single vessel and could find no emboli anywhere. There was, as Dr. Pittman suggested, congestion, which apparently increased markedly within four or five days.

DR. TOMCHIK: Was there anything to account for the appearance of the right middle lobe on the first films?

DR. CASTLEMAN: I think it may have been fluid. Could that shadow in the films be fluid between the lobes; would that give this picture?

DR. TOMCHIK: No; it is not in the proper location.

A PHYSICIAN: Is that the so-called "vanishing tumor" — loculated fluid in the fissure?

DR. CASTLEMAN: According to Dr. Tomchik, that is not in the right place for fluid between the lobes.

DR. TOMCHIK: There is no suggestion of a localized effusion within the fissures. Such an effusion should give a typical appearance on the lateral views.

DR. CURRENS: Were there occlusions of the coronary arteries?

DR. CASTLEMAN: They were extremely narrow and pin point; we did not find evidence of a fresh occlusion, but that is so often the case.

DR. WILLIAMS: Was there hemorrhage in the pericardial sac?

DR. CASTLEMAN: No; there was one little plaque of hemorrhage but that was not important. I do not think that the Dicumarol produced any change.

DR. FRIEDLICH: Were there areas of pulmonary hemorrhage or just localized areas of intense congestion?

DR. CASTLEMAN: There was no hemorrhage, just areas of congestion. The patient was having hemoptyses at one time; I suppose if we made more blocks of the lung, we might find hemorrhage in some alveoli.

CASE 42352

PRESENTATION OF CASE

An eighty-three-year-old man was admitted to the hospital because of abdominal pain.

During the day before entry there was a sudden onset of severe, persistent abdominal pain that caused him to collapse on the next day.

Four years previously he had a pneumococcal pneumonia of the left lower lobe that was successfully treated with penicillin. At that time cardiac enlargement and atrial fibrillation were noted. The blood pressure was 120 systolic, 60 diastolic. An electrocardiogram showed atrial fibrillation, left-axis deviation and minor T-wave changes. He subsequently remained in good health and took digitalis regularly. There was no history of diabetes mellitus.

Physical examination showed an acutely ill, dehydrated man with mottled cyanosis of the skin. The chest was emphysematous, and the breath sounds were distant. The heart was slightly enlarged to the left. There was atrial fibrillation. A Grade 2, systolic murmur was audible at the base. Examination of the abdomen revealed a board-like tenseness with rebound tenderness and marked spasm, mostly in the upper quadrants. No masses were felt. The abdomen was tympanitic throughout, and no bowel sounds were heard. The femoral pulses were +++ and

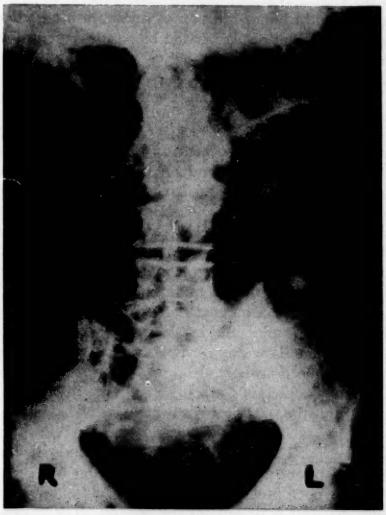

FIGURE 1. *Abdominal Film, Showing Multiple Distended Loops of Small Bowel as Well as Some Gas in the Colon.*

bounding. No pulses were palpable in the legs, which were cool and appeared mottled. Radial pulses were absent. Rectal examination was negative.

The temperature was 99.4°F., the pulse 78 and irregular, and the respirations 24. The blood pressure was 80 systolic, 40 diastolic.

The urine gave a +++ test for albumin; the sediment contained 50 red cells, 20 white cells and an occasional granular cast per high-power field. Examination of the blood revealed a hematocrit of 39 per cent and a white-cell count of 7300. The nonprotein nitrogen was 45 mg., the calcium 4 and

4.4 mg., and the fasting blood sugar 153 mg. per 100 ml. The sodium was 140 milliequiv., the potassium 4.4 milliequiv., the chloride 102 milliequiv., and the carbon dioxide 14 milliequiv. per liter. The amylase was 168 Russell units. A formed stool specimen gave a negative guaiac test. An x-ray film of the chest showed moderate elevation of both leaves of the diaphragm; the lungs appeared clear; there was some prominence of the heart in the region of the left ventricle. An abdominal film demonstrated multiple, distended, gas-filled loops of small intestine with fluid levels throughout the abdomen (Fig. 1); no distention of the colon was noted; changes consistent with Paget's disease were seen throughout the pelvis, especially on the right. An electrocardiogram showed no significant changes from those previously noted.

An abdominal paracentesis yielded feculent-smelling air. Another paracentesis yielded air and about 25 ml. of serosanguineous fluid with a hematocrit of 8 per cent and an amylase of 1200 Russell units. In spite of intravenous infusion of fluids, gastric suction and transfusions of plasma and blood the patient died six hours after admission.

Differential Diagnosis

Dr. William V. McDermott, Jr.*: This elderly man had evidence of degenerative arterial disease of the heart and kidneys and an acute abdominal catastrophe, which terminated in death within twenty-four to thirty-six hours. Before discussing the nature of the catastrophe, we might have Dr. Hanelin show the x-ray films. I am looking primarily for the presence or absence of free air in the abdomen, particularly in view of the findings at paracentesis.

Dr. Joseph Hanelin: The abdominal films, consisting of the supine and left-lateral-decubitus projections, do not show any obvious free air. In the decubitus projection there are a few radiolucent streaks that might represent retroperitoneal air. In the films taken with the patient erect, which include the chest and upper abdomen, there is no free air below the diaphragm. There are multiple gas-distended loops of small bowel and some air in the large intestine, which is not distended (Fig. 1). A fair amount of fecal material is present in the rectum. The distention is generalized in the small bowel, although it does preponderate in the upper two thirds of the abdominal cavity. There is extensive Paget's disease.

Dr. McDermott: There is a puzzling contradiction, which I shall try to resolve. Apparently, a fair amount of free air was obtained by paracentesis; yet the x-ray examination failed to demonstrate any significant amount of free air.

In an elderly man with this type of catastrophic episode in the abdomen, I should consider crises of vascular origin, such as ruptured dissecting aneurysm and superior mesenteric arterial thrombosis or embolization, but these seem unlikely in view of the total picture. The elevated amylase in the blood and peritoneal fluid suggests an acute hemorrhagic pancreatitis, particularly since it was associated with a low calcium level in the blood. Before seeing the x-ray films, I had thought that the accumulated evidence pointed to a perforating lesion of the upper gastrointestinal tract, with a diffuse spreading peritonitis, and was considering the type of perforation that could cause death within thirty-six hours or less. Statistically, a perforation of a duodenal ulcer is the most common, but one would not expect death to occur so rapidly nor the peritonitis to produce feculent-smelling air.

Could this have been a perforated carcinoma or diverticulum of the lower gastrointestinal tract? There were no prodromal symptoms, and the evidence seems to be against disease of the large bowel. Certainly, the guaiac test on the stool was negative, and there was no indication in the x-ray examination of partial obstruction of the large bowel, such as one might expect with a carcinoma or diverticulitis with free perforation into the peritoneal cavity. The significant findings were an abdominal catastrophe, which was fatal within twenty-four to thirty-six hours; a clinical picture of a virulent spreading peritonitis; free air, which was feculent-smelling; and elevated amylase in the blood and peritoneal fluid, associated with a low serum calcium. If there had been free air in the peritoneal cavity on x-ray examination, this would certainly have pointed to a perforation of the upper gastrointestinal tract with attendant release of pancreatic enzymes or even an associated severe pancreatitis, which is not uncommon and which may obscure the diagnosis of upper gastrointestinal disease. Because of the air removed during paracentesis, one would think in terms of a gastrointestinal perforation, but the findings in the x-ray films are a contradiction of that. If there had been free air in the peritoneal cavity, demonstrated by paracentesis to this extent, it certainly should have been seen in the x-ray examination. Is that true, Dr. Hanelin?

Dr. Hanelin: Yes, it is.

Dr. McDermott: I had thought that no films had been taken in the upright position and that that, therefore, might explain the discrepancy since free air in the peritoneal cavity is difficult to demonstrate unless a decubitus projection or a film with the patient upright is taken. But since the x-ray examination was adequate, I shall have to revise my initial opinion on the subject and say that the needle during paracentesis probably penetrated a tense, distended gastrointestinal loop. Although that is not common, that is the only way that I can resolve the apparent contradiction between the findings during paracentesis and on x-ray examination. Obviously, the diagnosis hinges on that since in the absence of free air in the peritoneal cavity I should make a diagnosis of primary hemorrhagic pancreatitis rather than of a perforating lesion of the upper gastrointestinal tract.

*Assistant surgeon, Massachusetts General Hospital.

The elevated amylase in the blood and in the peritoneal fluid and the low calcium are not inconsistent with a lesion of the upper gastrointestinal tract other than primary hemorrhagic pancreatitis. I see no reason why in cases of perforating duodenal ulcer or even perforating carcinoma of the gastric antrum, in which the amylase in the blood and in the peritoneal fluid is high, there may not occasionally be a concomitant reduction in the serum calcium, which is usually explained on the basis of the release of fatty acids and its conjunction with calcium to form soaps.

If I explain the air obtained on paracentesis on the basis of penetration of the bowel by the introduced needle, I shall conclude with a diagnosis of acute hemorrhagic pancreatitis, which characteristically occurs catastrophically and terminates in death, with peripheral vascular collapse within a short time — certainly, thirty-six hours is not inconsistent with this diagnosis. The other conditions present, which had little relation to the primary disease, were arteriosclerotic heart disease and probably nephrosclerosis of the kidney. I did not discuss the urinary-tract findings, because they did not seem relevant to the primary problem; they may have represented chronic prostatitis in an elderly man who probably also had some degree of nephrosclerosis.

DR. BENJAMIN CASTLEMAN: Would anyone like to quiz Dr. McDermott on any of his statements?

DR. CHESTER M. JONES: I think that his diagnosis seems to be reasonable. The only other condition that might give an unusually high serum amylase is perforated ulcer. If there was a perforated ulcer, free air should have been found in the x-ray films. Moreover, there was no preceding history of an ulcer. I should think that the hemorrhagic pancreatitis, with paralytic ileus as a result of whatever was going on in the peritoneal cavity, was the most reasonable diagnosis.

DR. CASTLEMAN: Dr. Ingelfinger, have you a comment?

DR. FRANZ INGELFINGER: I, too, agree with the diagnosis. I have not heard of a calcium as low as this produced by peritoneal absorption of pancreatic enzymes from a perforated viscus, and this is classic of acute pancreatitis. The serosanguineous fluid would also be difficult to explain on the basis of perforation.

A PHYSICIAN: Is mottled cyanosis likely to occur in pancreatitis?

DR. MCDERMOTT: I think that might occur in the terminal phase of any acute catastrophic disease, with peripheral vascular collapse. It is seen commonly in the severe form of acute hemorrhagic pancreatitis.

DR. CASTLEMAN: How often does one find distended loops of small bowel with acute pancreatitis?

DR. MCDERMOTT: Very commonly, within a very short time after onset a severe, paralytic ileus with a distended tympanitic abdomen can develop.

DR. JONES: It is characteristic of such an episode.

DR. CASTLEMAN: I do not recall ever having seen a paralytic ileus of this extent in patients with acute hemorrhagic pancreatitis at the autopsy table; of course, we see it in the late stages.

DR. MCDERMOTT: I agree with Dr. Jones that clinically it is quite characteristic after twenty-four hours.

DR. HANELIN: We see it commonly on x-ray films.

CLINICAL DIAGNOSES

Acute hemorrhagic pancreatitis.
Arteriosclerotic heart disease.

DR. WILLIAM V. MCDERMOTT, JR.'S, DIAGNOSES

Acute hemorrhagic pancreatitis.
Arteriosclerotic heart disease.
Nephrosclerosis.

ANATOMICAL DIAGNOSIS

Small-bowel obstruction, with gangrene, produced by adhesive band.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Autopsy showed that this man did not have pancreatitis. We do not know how to explain all the chemical findings. I asked the question about distended bowel loops because this was small-bowel obstruction: a loop of ileum beginning 20 or 30 cm. from the ileocecal valve was caught between an adhesive band that extended from the medial aspect of the sigmoid across medially to the posterior wall of the pelvis. A loop of small bowel about 20 cm. long had extended through the band and twisted on itself, producing gangrene of the bowel. There was about a liter of hemorrhagic fluid but no frank peritonitis.

DR. MCDERMOTT: No free air?

DR. CASTLEMAN: No.

DR. MCDERMOTT: The needle must have penetrated the bowel.

DR. CASTLEMAN: I am sure that that is what happened.

DR. MCDERMOTT: I might mention that an elevated amylase in the blood has been shown by a series of studies to be associated occasionally with obstruction of the bowel. When the duodenum becomes distended from mechanical obstruction, it can cause enough increase in pressure secondarily in the pancreatic-duct system to produce a high level of amylase in the blood. These studies* have clarified to some extent the puzzling findings of an elevated amylase with intestinal obstruction. I must say, like Dr. Ingelfinger, that I am surprised that the serum calcium was depressed so much.

*Boyd, T. F., and Byrne, J. J. Elevated serum amylase in intestinal obstruction. Presented at a meeting of the Boston Surgical Society, Boston, March 26, 1956.

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SUBSCRIPTION TERMS: $8.00 per year in advance, postage paid, for the United States (residents, interns and medical students, $5.00 per year); Canada, $9.00 per year (Boston funds); foreign, $10.50 per year. Long-term rates: United States, 2 years $15.00, 3 years $22.00; Canada, 2 years $17.00, 3 years $25.00; foreign, 2 years $20.00, 3 years $29.50.

MICROFILM volumes available to regular subscribers through University Microfilms, 313 N. First Street, Ann Arbor, Michigan.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

WHAT PRICE SECURITY?

ON August 1, President Eisenhower announced that he had signed H. R. 7225, the Social Security amendments of 1956, and pointed out that "Although there were differences of opinion over separate provisions, the final legislation was approved overwhelmingly by Congress. In signing this legislation, I am hopeful that this new law, on the whole, will advance the economic security of the American people."

Differences of opinion were centered mostly on the provision in the bill making totally and permanently disabled persons eligible to receive their Social Security retirement benefits at age fifty instead of age sixty-five. The American Medical Association, as reported previously in these columns, had opposed the compulsory cash disability benefits and had urged that there should be a thorough social and economic study of the entire social-security system before it was further enlarged.

The Administration had also opposed the cash disability provision, and Secretary Folsom, of the Department of Health, Education and Welfare, speaking before the Senate Finance Committee last March, had stated that:

> There is a great divergence of opinion on the difficulties of administering a cash disability program, our ability to control the costs, and the effects on vocational rehabilitation. On the other hand, we are making significant progress in helping disabled people — through assistance payments to the needy, the rehabilitation program, and the disability freeze. We need more time to develop these programs fully and evaluate their results.
>
> In view of the grave uncertainties involved and the potential heavy costs to all social taxpayers, I would advise the committee not to adopt the provision of H. R. 7225 for cash disability benefits.

In May, the Senate Finance Committee reported out the bill with the disability-payments section deleted. A compromise amendment, however, was later presented to the Senate, the amendment being essentially the same as the deleted section except that the increased OASI payroll taxes to finance the payments would be put in a separate trust fund and disbursed from there. This version passed the Senate on July 17 by a 47-45 vote. As a result, beginning on January 1, 1957, OASI taxes will be increased one quarter of 1 per cent for employer and employee, and three-eighths of 1 per cent for the self-employed. Disability benefits will begin on July 1, 1957.

Also under H. R. 7225, employed women and wives of retired workers may have the choice of accepting reduced benefits at age sixty-two or obtaining full benefits at sixty-five. Widows of covered workers are allowed full benefits at age sixty-two; this being the first time that the age-sixty-five-retirement requisite has been broken since the Social Security Act was passed in 1935.

As finally adopted, H. R. 7225 also extends social-security coverage to about 600,000 additional farm owners or operators and about 225,000 self-employed lawyers, dentists and osteopaths. Doctors of medicine

are now the only professional group excluded from OASI coverage, their exclusion still conforming to the wishes of the American Medical Association as reaffirmed by the House of Delegates in Chicago in June.

Having become the law of the land (Public Law 880, 2nd Session, 84th Congress), H. R. 7225 has, therefore, through its cash-for-disability provisions and lowered retirement age, established precedents that to the medical profession are highly significant symptoms of an economic—and moral—malady. The medical profession is certainly not opposed to the Federal social-security program, which is to millions of employed Americans their only source of retirement security, but it cannot help being demonstrably disturbed over Federal encroachment on the practice of medicine via social-security legislation. And, as responsible citizens, doctors of medicine cannot help but be alarmed at the constant amendments to the Social Security Act made without regard for the ultimate soundness and stability of the program.

The American Medical Association's plea for a careful, exhaustive, and nonpartisan study of the entire social-security system before further extension of benefits is legislated is one that should be seriously considered by the senators and representatives who will comprise the 85th Congress and who may be expected to have at heart the economic and social stability of the nation and the need for a strong financial foundation on which individual safeguards may be built.

The basic theory of social security makes it a noble experiment in the efforts of man to come to better terms with his environment. The very word "security," however, as used today, is coming to imply a condition that can hardly be produced on a national scale without the loss of something still more valuable. The price may be the capacity and the desire to work and if necessary to suffer for the preservation of one's self-sustaining status—to overcome on one's own account the difficulties of the passage through life. For he that overcometh will be made a pillar in the temple.

The one thing that the protective state has never yet achieved is protection; the best that it can hope to offer is freedom of individual opportunity.

IODIDE MUMPS

Elsewhere in this issue of the *Journal* Sussman and Miller describe 2 cases of parotid-gland swelling that followed the intravenous injection of sodium diatrizoate (Hypaque) and sodium methylglucamine diacetylamino-triiodobenzoates (Renografin). Although swelling of the parotid gland has long been known to occur occasionally after the long-term administration of iodide it is of interest that, in these cases, it apparently followed acute exposure to iodine-containing compounds used as contrast mediums.

Both the responsible agents are organic compounds containing 59.87 per cent and 36.94 per cent of iodine respectively. Other organic iodine-containing compounds in common use contain as much as 65.8 per cent of iodine. In the everyday use of these high-iodine-containing compounds it is not unusual to administer as much as 10 gm. of organically bound iodine at one quick injection. Usually, this iodine is firmly bound, but undoubtedly, depending on the compound and the length of exposure to it, varying amounts are split off by the body and converted into iodide.

Although in man as much as 8.5 gm. of iodide slowly given intravenously as sodium iodide is usually tolerated, it is possible to produce serious toxic effects with much smaller amounts in the presence of renal impairment or individual idiosyncrasies.

Apparently, in some patients, the amount of iodide freed, or perhaps the irritant properties of the organic iodine-containing preparation itself, is capable of producing parotitis and possibly other signs of iodide toxicity not yet observed or reported. It would be interesting to know whether mucous-membrane irritability, rhinorrhea, conjunctivitis, skin rashes and other iodide reactions appear, in perhaps fleeting fashion, from the use of these preparations.

Any iodide released by these preparations is, for the most part, excreted by the kidney. Therefore, it is conceivable that in the presence of renal impairment toxic levels of iodide might rapidly accumulate.

Since these agents are finding ever-increasing use in many diagnostic procedures it is apparent that care must be taken if more serious iodide reactions are to be avoided.

UNDERSTANDING THE ALCOHOLIC

The process of fermentation became a problem of mankind, probably long before Shem and Japhet covered their drunken father's nakedness, and the art of the distiller has done little to abate it. Attempts have been made over the years to break the spell that drink has cast upon the Western world, but, based on emotionalism and duress, they have been largely ineffective. Only the faith of Islam seems to have been relatively successful in controlling this desire and quenching the thirst.

Psychiatry and pharmacology and the consideration of the drunkard as a person who is ill or unfortunate, rather than as one who is wicked or contemptible, have opened up a new concept of the problem in recent years, and in very recent years new methods of meeting it have been elaborated. The occurrence of drunkenness will no more be abolished than the use of alcohol will be or should be banned, but it is reasonable to hope that eventually the first will be cut down and the second brought under reasonable control.

Among the many agencies that are now working

for the control of alcoholism the Boston Committee on Alcoholism is prominent in this area and has recently announced its fifth annual fifteen-week educational program. This program, intended for hospital staff members and personnel officials, will be given under the direction of Dr. David Landau with the cosponsorship of the Greater Boston Chamber of Commerce.

The course will be presented at Boston University, where it was started in 1952, the first session taking place on Wednesday, September 19, 1956, at 7:15 p.m. It will be a combination of lectures and seminars, intended to instruct in the understanding and assistance of employees whose efficiency is affected by their drinking.

MASSACHUSETTS PUBLIC HEALTH ASSOCIATION

THE publicity committee of the Massachusetts Public Health Association has announced, in a 2-color appeal under the title "Memorabilia," that the annual fall meeting of the Association will be held in Amherst on September 7 and 8, 1956. Members of the Association may consider the notice as a summons; all others as a cordial invitation.

Memorabilia ("things remarkable and worthy of remembrance or record," according to Noah Webster, who made the principal address when Amherst College was dedicated in September, 1821) refer to the historic association of Amherst with the seventh month of the ancient Roman calendar. Thus, in September, 1775, the militiamen of Amherst arrived home from the Battle of Bunker Hill (June 17) and received a penny a mile for transportation. In September, 1849, a bill for the establishment of an agricultural college on land costing 80 cents an acre passed the General Court; in September, 1871, the recluse poetess, Emily Dickinson, made a public appearance to the extent of handing cookies from her pantry window to the neighboring children, and in September, 1900, — *mirabile dictu* — the Lord Jeffrey Inn was still in business as it is today.

On a more technical level, the meeting will come to order at 11 a.m. on September 7, with Dr. Robert H. Hamlin, health director of Brookline, presiding over the general session. Among the subjects to be discussed will be the merits of compulsory hospitalization of the tuberculosis patient, school health education, milk control, household sewage-disposal systems and problems of suburban health.

The after-dinner speech on September 7 will consist of an acknowledgment by Fillmore H. Sanford, Ph.D., associate director for scientific studies of the Massachusetts Joint Commission on Mental Illness and Health, that "Public Health People Are Puzzling." Dr. Alfred L. Frechette, president of the Association, will preside.

The Senate of the University of London has decided not to confer medical degrees on candidates of the female sex.

Boston M. & S. J. *September 4, 1856*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

THOMPSON — Charles E. P. Thompson, M.D., of Fairhaven, died on July 30. He was in his seventy-seventh year.

Dr. Thompson received his degree from Boston University School of Medicine in 1903. He was formerly school physician and town physician in Fairhaven. He was a fellow of the American Medical Association.

WARREN — Thomas F. Warren, M.D., of Fall River, died on July 5. He was in his seventy-ninth year.

Dr. Warren received his degree from Baltimore Medical College in 1905. He was formerly surgeon of the Fall River Police Department and a fellow of the American Medical Association.

He is survived by his widow and a half-brother.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

Orthopedic Clinic	Date	Clinic Consultant
Haverhill	September 5	William T. Green, M.D., and Henry Banks, M.D.
Greenfield	September 6	Charles L. Sturdevant, M.D.
Lowell	September 7	Albert H. Brewster, M.D.
Salem	September 10	Paul W. Hugenberger, M.D.
Gardner	September 10	Carter R. Rowe, M.D.
Lynn*	September 10	Daniel M. Killoran, M.D., and John J. Crowley, M.D.
Brockton	September 13	George W. Van Gorder, M.D.
Pittsfield	September 19	Edward J. Coughlin, Jr., M.D.
Worcester	September 21	John W. O'Meara, M.D.
Fall River	September 24	David S. Grice, M.D., and Arthur W. Trott, M.D.
Springfield	September 25	James D. Fisher, M.D.
Hyannis	September 27	Paul L. Norton, M.D.

Rheumatic-Fever Clinic	Dates
North Reading	September 4, 11, 18, 25
Fitchburg	September 5, 12, 19, 26

Plastic Clinic	Held	Consultant
Eastern Massachusetts	Semi-monthly	Bradford Cannon, M.D., and Joseph E. Murray, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Clinic.

SERVICES OF THE DIAGNOSTIC LABORATORY

A new edition of *Services of the Diagnostic Laboratory* has just been prepared. It contains complete information on the various bacteriologic, virologic, and mycologic diagnostic tests performed by the Laboratory for the physicians of the Commonwealth. Information is included on the proper collection and submission of specimens and suggestions are given on the usefulness of many of the tests. Physicians wishing to have a copy of the booklet should write to the Massachusetts Department of Public Health Diagnostic Laboratory, 281 South Street, Jamaica Plain 30, Massachusetts.

CORRESPONDENCE

REGARDING BENEDICT'S TEST

To the Editor: The article, "Significance of an Opaque, Green Benedict Reaction," by William T. Wright in the March 22 issue of the *Journal* will confuse your readers in the use of Benedict's test because it is based on an incorrect timing of the test. Benedict did not recommend three minutes over a flame as stated by the author. The reference cited clearly indicates two minutes. The equivalent of two minutes' flame time is three minutes in a water bath.

MEYER SAMSON, *Director*
Samson Laboratories
Philadelphia

Note: In Benedict's communication published in the *Journal of the American Medical Association* (October 7, 1911) he states, regarding the use of his reagent, that "until one is familiar with its behavior the following directions should be closely adhered to." He goes on to say that after the urine has been added to the reagent the mixture is heated to vigorous boiling, kept at this temperature for one or two minutes and allowed to cool spontaneously.—ED.

CAREFUL READER

To the Editor: I am an inveterate reader of your excellent journal, and an occasional reader of the *New Yorker*. Regarding the first article in your issue of June 7, in the style of the latter journal: "What Page Do You Read?"

On p. 1055: "We were indeed surprised to find that the serum of 1 showed a 1:4 reaction when the yeast-phase antigen of *H. capsulatum* was titrated against it."

On p. 1057: "Therefore, when we observed pertinent findings in only 2 of the cases tested — namely, a reaction of 1:4 and 1:14 when the serum was titrated against the yeast phase, or standard antigen of *H. capsulatum*, respectively — this fact was not viewed by us with any degree of surprise."

Co-authors divided,
Like the house in the mot;
Joress surprised,
Bushueff is not.

Positions reversed —
Bushueff amazed;
Now Joress is cool
And cannot be fazed.

L'Envoi

'Tis very plain to see
What always must be:
Scientists never
Will get together.

HERBERT M. RUBINSTEIN, M.D.
Michael Reese Hospital
Chicago

ERRATUM

To the Editor: An error appeared in a footnote in the *Journal* of August 2, 1956, page 238. The volume of the *Journal* referred to should be 254 and not 256.

L. A. GINNEBAUGH
Battle Creek, Michigan

Note: So eager are the editors to be thoroughly up-to-date that they projected into the future the reference noted by Mr. Ginnebaugh. Volume 256 will be published during the first six months of 1957.—ED.

SUSPENSION OF LICENSE

To the Editor: At a meeting of the Board of Registration in Medicine held July 10, 1956, it was voted to suspend the registration of Dr. Jacob Abrams, 562 Shirley Street, Winthrop, Massachusetts, for five months.

ROBERT C. COCHRANE, M.D., *Secretary*
Board of Registration in Medicine
State House
Boston

REVOCATION OF LICENSE

To the Editor: At a meeting of the Board of Registration in Medicine held July 10, 1956, it was voted to revoke the registration of Dr. Daniel Lee Berni, Cambridge and Somerville, Massachusetts.

ROBERT C. COCHRANE, M.D., *Secretary*
Board of Registration in Medicine
State House
Boston

RESTORATION OF LICENSE

To the Editor: At a meeting of the Board of Registration in Medicine held July 10, 1956, it was voted to restore the registration of Dr. Thomas F. Beatty, 33 Hollywood Road, West Roxbury, Massachusetts.

ROBERT C. COCHRANE, M.D., *Secretary*
Board of Registration in Medicine
State House
Boston

NONCLINICAL NOTES

AMERICAN ELECTROENCEPHALOGRAPHIC SOCIETY

At the tenth annual meeting of the American Electroencephalographic Society, the following officers were elected: president, Dr. John R. Knott; president-elect, Dr. Robert S. Dow; secretary, Dr. J. K. Merlis; and treasurer, Dr. Peter Kellaway.

NOTICES

AMERICAN PSYCHOSOMATIC SOCIETY

The fourteenth annual meeting of the American Psychosomatic Society will be held at Chalfonte-Haddon Hall, Atlantic City, May 4 and 5, 1957.

Titles and abstracts of papers for consideration for the program should be received by the Program Committee no later than December 1, 1956. Twenty minutes will be allotted for presentation of each paper. Abstracts, in sextuplicate, should be submitted to the Chairman, 551 Madison Ave., New York 22, New York.

POSTGRADUATE TRAINING IN ADOLESCENT CARE

The Adolescent Unit of the Children's Hospital is offering a general practice-type of postgraduate training in the care of adolescents. One-year traineeships are available to a few properly qualified physicians having two or more years

of hospital experience after graduation from medical school. Dr. J. R. Gallagher will direct the teaching staff. Further information may be obtained from Dr. J. R. Gallagher, chief of the Adolescent Unit, Children's Hospital, Boston.

SOCIETY MEETINGS AND CONFERENCES

SEPTEMBER 3–5. Congress on Blood Transfusion, Blood Banks and Hematology. Page 297, issue of February 9.
SEPTEMBER 3–7. First Inter-American Conference on Occupational Medicine and Toxicology. Page 152, issue of July 19.
SEPTEMBER 5–27. Consultation Clinics for Crippled Children in Massachusetts. Page 446.
SEPTEMBER 8, 9 and 10. Vermont Heart Association and University of Vermont College of Medicine. Page 360, issue of August 16.
SEPTEMBER 9–13. International College of Surgeons. Page 304, issue of August 9.
SEPTEMBER 18. South End Medical Club. Page 402, issue of August 23.
SEPTEMBER 19 and 20. San Diego Postgraduate Assembly. Page 360, issue of August 16.
SEPTEMBER 27–29. University of Michigan Medical School. Page 402, issue of August 23.
SEPTEMBER 28 and 29. Mississippi Valley Medical Society and American Medical Writers' Association. Page 402, issue of August 23.
OCTOBER 4, 5 and 6. Academy of Psychosomatic Medicine. Page 402, issue of August 23.
OCTOBER 7, 8 and 9. New Hampshire and Vermont State Medical Societies. Page 304, issue of August 9.
OCTOBER 8–13. International Cancer Cytology Congress. Page 104, issue of July 12.
OCTOBER 15–26. New York Academy of Medicine. Page 304, issue of August 9.
OCTOBER 19 and DECEMBER 14, 1956, and FEBRUARY and APRIL, 1957. Massachusetts Society for Research in Psychiatry. Page 56, issue of July 5.
OCTOBER 30 and 31 and NOVEMBER 1. New England Postgraduate Assembly, Boston.
NOVEMBER 12–16. American Public Health Association. Page 402, issue of August 23.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, SEPTEMBER 6

THURSDAY, SEPTEMBER 6

8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building. Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.
*12:15–1:15 p.m. Tumor Clinic. Dr. T. W. Botsford. Amphitheater, Peter Bent Brigham Hospital.
*3:00 p.m. Thoracic Conference. Spontaneous Pneumothorax and Thoracic Emergencies. Dr. Harrison Black. Main Amphitheater, Peter Bent Brigham Hospital.

FRIDAY, SEPTEMBER 7

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Urological Conference. Dr. C. J. E. Kickham, presiding. Auditorium, Carney Hospital, Dorchester.
*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.

SATURDAY, SEPTEMBER 8

8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*8:30–10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*9:30–11:00 a.m. Surgical House Officers' Conference. Second-Floor Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Teaching Ward Rounds. Ward South 2, Free Hospital for Women.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

MONDAY, SEPTEMBER 10

8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. X-Ray Conference. Dr. William Carey. Saint Elizabeth's Hospital.
*3:00–4:00 p.m. Neuroradiologic Conference. Dr. Bertram Selverstone. Stearns Auditorium, New England Center Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Surgical Conference Room, Peter Bent Brigham Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.

TUESDAY, SEPTEMBER 11

8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical Grand Rounds. Pathology Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Medical Grand Rounds. Main Conference Room (Ground Floor), Lemuel Shattuck Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Pediatric Grand Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic. (Cafeteria) New England Deaconess Hospital.
*2:00–3:00 p.m. Hematology Conference. Dr. Mario Stefanini. Saint Elizabeth's Hospital.
*4:00–5:30 p.m. Anesthesia Conference. Dr. Benjamin Etsten. Stearns Auditorium, New England Center Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetric). Faulkner Hospital.

WEDNESDAY, SEPTEMBER 12

8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. Deaconess II, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Auditorium, Carney Hospital, Dorchester.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Boston State Hospital Psychiatry Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

*Open to the medical profession.